Pneumococcal Meningitis in Adults in 2014-2018 After Introduction of Pediatric 13-valent Pneumococcal Conjugate Vaccine in Japan

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Abstract

We assessed the impact of pediatric 13-valent pneumococcal conjugate vaccine (PCV13) on pneumococcal meningitis in adults in Japan in 2014-2018 by comparing epidemiological characteristics of adults with invasive pneumococcal disease with (n=222) and without (n=1,258) meningitis. Pneumococcal meningitis annual incidence in 2016-2018 was 0.20–0.26 cases/100,000 population. Age ($p<0.001$) and case fatality rate ($p=0.003$) were significantly lower in patients with meningitis than in those without meningitis. Meningitis risk was higher in asplenic/hyposplenic or splenectomized patients (adjusted odds ratio [aOR] 2.29, 95% CI 1.27–4.14), for serotypes 10A (aOR 3.26, 95% CI 2.10–5.06) or 23A (aOR 3.91, 95% CI 2.47–6.19), but lower for those aged ³65 years (aOR 0.59, 95% CI 0.44–0.81). PCV13 had an indirect effect on nonmeningitis, but its impact on meningitis was limited because of an increase in non-PCV13 serotypes. Of meningitis isolates, 78 (35.1%) and 3 (1.4%) were penicillin G- and ceftriaxone-resistant. We also confirmed association of the *pbp1b*A641C mutation with meningitis (aOR 2.92, 95% CI 1.51–5.65).

Introduction

Streptococcus pneumoniae colonizes the nasopharynx asymptomatically, and often causes pneumococcal disease in children and adults[1,2]. Occasionally, it can enter the bloodstream and cause invasive pneumococcal diseases (IPD) such as meningitis and bacteremia[3,4]. *S. pneumoniae* is the most common cause of bacterial meningitis in children and adults, and causes serious sequelae and death[5–7]. In 2015, there were estimated to be 83,900 cases and 37,900 deaths in children caused by pneumococcal meningitis worldwide[8]. Of all deaths caused by pneumococcal infection, meningitis is estimated to account for 12%. Up to 30% of survivors have some type of neurological or neuro-behavioural sequences[9]. These include seizures, hearing loss and vision loss, cognitive impairment, neuromotor disability and memory or behavior changes. A recent genome-wide association study from the United States reported a significant association of the *pbp1b*A641C mutation with the clinical occurrence of meningitis in patients with IPD, but there is no evidence that this mutation results in β-lactam resistance[10]. However, it is unclear whether the *pbp1b*A641C mutation is associated with meningitis in adult patients with IPD in Japan.

The incorporation of pneumococcal conjugate vaccines (PCVs) into infant immunization programs worldwide resulted in significant reductions ranging from 41–97% in the vaccine-type IPD, including pneumococcal meningitis, in children and older age groups[11]. In Japan, PCV7 was introduced for children under the age of 5 in November 2010, and subsequently included in the national immunization program in April 2013. It was then replaced by 13-valent PCV (PCV13) in November 2013, and the vaccination rate of PCV13 was approximately 90% in 2014. A significant reduction in the incidence of PCV7-type IPD in children under 5 was reported in Japan after the introduction of PCV7[12], although the incidence of IPD in children caused by nonvaccine serotypes increased. In 2014, a 23-valent pneumococcal polysaccharide vaccine (PPSV23) was included in the national immunization program for adults aged ≥65 years, while

PCV13 was licensed for adults ≥65 years in 2014, and became available on a voluntary basis. We conducted an enhanced surveillance of IPD in adults in Japan from 2013 to 2015, and found an indirect effect of the use of the pediatric PCV7 on the epidemiology of adult IPD[13]. Although the epidemiological and bacteriological characteristics of pneumococcal meningitis have been recently reported from Israel, England, and Wales[14,15], the epidemiological features of meningitis have not been fully investigated in adult patients with IPD in Japan.

In this study, we characterized the epidemiological features of pneumococcal meningitis in adults in Japan between 2014 and 2018, and assessed the impact of pediatric PCV13 on this disease.

Results

Clinical Characteristics of IPD

The number of IPD cases per 100,000 population in adults gradually increased during 2014 to 2015, and plateaued during 2016 to 2018. Therefore, we estimated that the annual incidence of IPD and pneumococcal meningitis in adults was 1.40–1.98 cases and 0.20–0.26 cases/100,000 population during 2016 to 2018 (Table 1). A total of 1,480 IPD cases were classified as meningitis (n = 222) and nonmeningitis (1,258). Of the 222 cases of meningitis, 174 (78.4%) were culture-positive for bacteria in CSF, 10 (4.5%) were positive for antigen in CSF, and 38 (17.1%) were positive for blood culture and were associated with typical meningeal signs. Meningitis cases accounted for 15.0% of the total IPD cases (222/1,480). The proportion of meningitis cases to total IPD cases (21.0%; 98/467) in patients aged 15–64 years was significantly higher than that (12.2%; 124/1013) in patients ≥65 years ($p < 0.001$).

The clinical characteristics of patients with meningitis and nonmeningitis IPD were compared (Table 2). The proportion of men was 59.7%. The median age (range) of patients with meningitis (66 years; age range; 15–100 years) was significantly lower than that of those with nonmeningitis (72 years; age range; 16–103 years; $p < 0.001$). The case fatality rate (CFR) was significantly lower for meningitis than for nonmeningitis ($p = 0.003$), although the difference between two groups was not significant when the patients were divided into two age groups. By contrast, the proportion of asplenic/hyposplenic or splenectomized patients was significantly higher for meningitis (9.5%) than for nonmeningitis (3.0%) ($p < 0.001$). Although the proportion of IPD patients with a history of PCV13 vaccination was only 0.3%, the proportion with a history of PPSV23 vaccination was approximately 10%. No difference was found in the rates of vaccination with PCV13 or PPSV23 between meningitis and nonmeningitis patients.

Association of Variables with Risk of Meningitis

We next analyzed variables including age ≥65 years, asplenia/hyposplenia or splenectomy, and major serotypes to determine whether they were significantly associated with meningitis after adjusting for confounders (Table 3). The two most common serotypes of meningitis cases were 10A (17.6%) and 23A

(16.7%). While the odds of meningitis were higher for asplenic/hyposplenic or splenectomized patients (adjusted odds ratio [aOR] 2.29, 95% CI 1.27–4.14) and for serotypes 10A (aOR 3.26, 95% CI 2.10–5.06) or 23A (aOR 3.91, 95% CI 2.47–6.19), they were lower for age ≥65 years (aOR 0.59, 95% CI 0.44–0.81) or serotype 19A (aOR 0.20, 95% CI 0.07–0.56).

Vaccine Coverage

The percentages of PCV13 or PPSV23 serotypes within pneumococcal isolates, stratified by isolation year and disease type, are shown in Figure. Over all cases of IPD, the percentages of PCV13 serotypes significantly decreased over the study period ($p < 0.001$), although no between-year differences were found in the percentage of PPSV23 serotypes. By contrast, no significant between-year differences were found in the percentages of PCV13 serotypes in the meningitis cases, even with the gradual decrease in the percentages of PCV13 serotypes during the study period. The percentages of PPSV23 serotypes in meningitis cases also did not differ over the study period. However, the percentages of PCV13 ($p < 0.001$) or PPSV23 serotypes ($p < 0.048$) significantly decreased during the study period in nonmeningitis cases.

Antimicrobial Susceptibility

A total of 1,476 strains were examined for antimicrobial susceptibility (Table 4). Of the meningitis cases (n = 222), a total of 78 strains (35.1%) were resistant to PCG. By contrast, of the nonmeningitis isolates (n = 1,254), 14 strains (1.1%) showed intermediate resistance (n = 9) or resistance (n = 5) to PCG. All the meningitis strains with serotypes 23A (37 strains) and 15A (14 strains) were resistant to PCG, and strains resistant to PCG were detected for several other serotypes including 35B, 6C (Appendix Figure). Three meningitis strains were ceftriaxone resistant, but no meropenem-resistant strain was found. All meningitis strains were susceptible to vancomycin. The MIC_{50} and MIC_{90} values were similar for meningitis and nonmeningitis strains for all antimicrobial agents tested.

Association of the *pbp1b*A641C Mutation with Meningitis

We evaluated the effect of the *pbp1b*A641C mutation on the risk of meningitis using mixed-effects logistic regression explicitly controlled for patient age group, pneumococcal serotype, and susceptibility to three β-lactam antibiotics (Table 5). The odds of causing meningitis were higher for strains bearing the *pbp1b*A641C mutation (aOR 2.92, 95% CI 1.51–5.65), but lower for patients aged ≥65 years (aOR 0.55, 95% CI 0.40–0.74). We also evaluated whether the *pbp1b*A641C mutation was associated with the susceptibility to PCG of both meningitis and nonmeningitis isolates (Appendix Table 2). The presence of the *pbp1b*A641C mutation was significantly associated with PCG resistance for meningitis isolates ($p < 0.001$), but not for nonmeningitis isolates ($p = 0.683$).

Discussion

In the present study, we determined the annual incidence of pneumococcal meningitis in adults in Japan during the period 2016–2018. The incidence of pneumococcal meningitis in patients aged 15–64 years and ≥65 years remained unchanged during this period. The incidence of pneumococcal meningitis (0.20 cases/100,000 population) in adults in 2016 was approximately four times lower than that (0.85) reported in Israel in 2014–2015, and comparable to that (0.29) in England and Wales in 2015–2016[14,15]. We also found that the CFR of adult patients with IPD was significantly lower for those with meningitis (9.9%) than for nonmeningitis cases (17.6%), which is consistent with a report from Israel[14]. The lower CFR of adult patients with meningitis in our study may be partially explained by the significantly lower age of adult patients with meningitis compared with those with nonmeningitis.

Our study also demonstrated that the proportion of asplenic/hyposplenic or splenectomized adult patients with meningitis (9.5%) was significantly higher than for those with nonmeningitis (3.0%), as was the aOR of meningitis. Collectively, our data indicate that impaired splenic function may increase the risk of meningitis irrespective of the infecting serotype or the patient's age. It is well known that asplenic or hyposplenic or splenectomized patients are at increased risk for fulminant infections with encapsulated bacteria; this is attributable to a lack of splenic filtering and decreased production of specific antibodies and memory B cells[16,17]. A recent study of 2,435 adult patients with IPD demonstrated that the proportion of asplenic patients with meningitis (6/37; 21.0%) was significantly higher than in patients with a spleen (112/2,398; 4.7%)[18]. The authors also reported that the proportions of asplenic patients requiring intensive care admission or mechanical ventilation use and suffering acute kidney injury were significantly higher than for patients with a spleen, although the difference in the CFR between the two groups was not significant. These findings confirmed that asplenic patients had more severe IPD than patients with a spleen.

We also found significantly higher odds of meningitis in patients infected with serotypes 10A or 23A, which are not included in PCV13. A recent study in England and Wales reported similar findings of significantly increased odds of meningitis with serotypes 10A, 23B, and 35B[15]. Another study from Israel also demonstrated that the percentage of adult patients with meningitis was significantly higher for IPD caused by serotypes 24F, 23F, 15B/C, 23B, or 23A[14]. These findings indicate that the serotypes that commonly cause meningitis in adults include both types contained in PPSV23 (such as 10A and 15B/C) and nonvaccine types (such as 23A, 23B, 24F), plus 23F, and support the idea of the limited impact of pediatric PCV13 on meningitis in adults. A recent study from the Pneumococcal Serotype Replacement and Distribution Estimation project assessed the serotype distribution of the remaining serotypes involved in pneumococcal meningitis worldwide[19]. The study demonstrated the percentage of pneumococcal meningitis occurring after infection with serotypes included in the current PCV13 and upcoming PCV products including PCV20 or PCV24, for all cases of meningitis in locations using PCV13[20–23]. While the percentage of PCV13 serotypes was 14.8% for patients aged < 5 years and 25.2% for those aged ≥5 years, the percentages of PCV20 or PCV24 serotypes were 56.5–57.3% and 61.4–63.4%, respectively, for patients of all ages[19]. The higher percentage of PCV20 or PCV24 serotypes in

cases of meningitis indicates that the higher-valency PCVs have the potential to prevent more cases of pneumococcal meningitis in children and adults.

Because the rate of vaccination with PCV13 in Japanese adults is currently negligible, the significant decrease of the percentage of PCV13 serotypes in all IPD cases during the study period suggests an indirect effect of pediatric PCV13 vaccination. Although no difference was found in the percentage of PPSV23 serotypes for total cases of IPD, a slight, but significant decrease was found in the percentage of PPSV23 serotypes in nonmeningitis cases, but not in meningitis cases. This may be because the indirect effect of PCV13 is more evident in nonmeningitis than in meningitis: although the percentage of PCV13 serotypes was significantly decreased in nonmeningitis cases, no significant difference was found in meningitis cases. This finding indicates that the indirect effect of pediatric PCV13 vaccination on meningitis in adults in Japan has a limited impact, probably because of an increase in cases caused by the non-PCV13 serotypes 10A or 23A. A study from Israel also reported that nonmeningitis IPD but not meningitis decreased after PCV13 implementation[14]. The authors suggested that this was because of an increase in cases caused by non-PCV13 serotypes. By contrast, a study in England and Wales reported that the replacement of PCV7 by PCV13 in 2010 decreased pneumococcal meningitis cases, mainly those caused by the additional serotypes included in PCV13, without any increase in cases caused by non-PCV13 serotypes[15].

In our study, 35.1% of pneumococcal isolates (n = 222) from patients with meningitis were PCG resistant. By contrast, only 0.7% and 0.4% of pneumococcal isolates (n = 1,254) from nonmeningitis cases showed intermediate resistance or resistance to PCG. The difference in the MIC values for PCG between meningitis and nonmeningitis cases was responsible for the different MIC breakpoints for PCG, because the values of MIC_{50} and MIC_{90} for each antimicrobial agent were similar for the two groups. Based on this finding of reduced β-lactam susceptibility, it may be advisable for clinicians to administer ceftriaxone or meropenem plus vancomycin for adult patients suspected of having pneumococcal meningitis until susceptibility results are reported[6,24]. Japanese investigators recently reported that all patients with pneumococcal meningitis were treated with two or more antibiotics[25]. In that study, antimicrobial treatment was frequently initiated with ceftriaxone, followed by sulbactam/ampicillin, tazobactam/piperacillin, and vancomycin.

The present study showed that the odds of meningitis were higher in the presence of the *pbp1b*A641C mutation (aOR 2.92, 95% CI 1.51–5.65), and lower for patients aged ≥65 years (aOR 0.55, 95% CI 0.40–0.74), although we also found a significant association between the *pbp1b*A641C mutation and PCG resistance. These data confirm the previously reported association of the *pbp1b*A641C mutation with meningitis[10].

This study has several limitations. First, 33.1% of all cases (n = 2,213) reported to the NESID from 10 prefectures during the study period were not enrolled in this study. Second, the reporting of some variables was incomplete for some enrolled cases. Therefore, the results of our study may not be fully representative of the population of interest. Third, abdominal computed tomography scans were not

examined for all enrolled cases to detect asplenia or hyposplenia. The clinical information about splenectomy may be inadequate. Therefore, we might have underestimated the number of IPD patients with asplenia/hyposplenia or splenectomy.

In conclusion, the incidence of pneumococcal meningitis in adults remained unchanged during 2016–2018. Patient ages and the CFR were significantly lower in meningitis cases than in nonmeningitis cases. The odds of meningitis were higher for asplenic/hyposplenic or splenectomized patients and for infection with serotypes 10A or 23A. An indirect effect of pediatric PCV13 on nonmeningitis cases in adults in Japan was evident, but its impact on meningitis cases was limited because of an increase in cases caused by non-PCV13 serotypes.

Materials And Methods

IPD Surveillance, Case Definition, and Bacterial Strains

The Adult IPD Study Group (https://www.niid.go.jp/niid/ja/ibi.html) conducted population-based surveillance of IPD in Japan from January 2014 to December 2018. IPD occurring in people over the age of 15 who live in 10 prefectures (Hokkaido, Miyagi, Yamagata, Niigata, Mie, Nara, Kochi, Fukuoka, Kagoshima, and Okinawa) was included in this surveillance. A case of IPD was defined as the detection of pneumococcus by bacterial culture or polymerase chain reaction (PCR) targeting *lytA*, or a positive test result for pneumococcal antigen in samples from normally sterile sites such as blood or cerebrospinal fluid (CSF) (*16*). We enrolled 1,480 cases of IPD during study period. All IPD cases were classified into two groups: meningitis or nonmeningitis. A meningitis case was defined as IPD with typical meningeal signs, and nonmeningitis as IPD other than meningitis. The annual incidence rates of IPD and pneumococcal meningitis were calculated based on the population denominators of the 10 prefectures obtained from the Statistics Bureau of Japan (*17*). When a case of IPD was reported to the Study Group, clinical information and the pneumococcal isolates were sent to the National Institute of Infectious Diseases (NIID). The clinical information included sex, age, smoking history, alcohol use, history of pneumococcal vaccination, current underlying diseases, immunocompromised conditions, asplenia/splenic hypoplasia (hyposplenia) or splenectomy, and outcome. Pneumococcal isolates were plated on blood agar and transferred to NIID. One isolate per case was included. Neither the laboratory methods nor the procedures of specimen collection have changed during the study period.

Serotyping and Antimicrobial Susceptibility Test

Because the serotype was determined directly from clinical samples using multiplex conventional PCR serotyping, pneumococcal isolates from three IPD cases were not serotyped (*18*). The serotype of the 1,477 culturable *S. pneumoniae* strains was determined using the Quellung reaction with anti-pneumococcal antisera (Statens Serum Institut, Copenhagen, Denmark) according to the manufacturer's protocol (*19*). Serotype 11A/E and nontypeable were determined as described previously (*20*). Because

one of the isolates did not grow on the agar plate before the antimicrobial susceptibility test, 1,476 strains were examined by the microbroth dilution method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. The minimum inhibitory concentration (MIC) breakpoints were determined for penicillin G (PCG), ceftriaxone, meropenem, and vancomycin according to the CLSI criteria (*21*).

Detection of Point Mutation in *pbp1b* Gene

Primer sequences, PCR amplification, and sequencing for detection of the *pbp1b*A641C mutation in 1,477 pneumococcal strains were performed as previously described (*9*).

Statistical Analysis

The demographic data and clinical characteristics of patients with meningitis and nonmeningitis IPD were compared using the χ test or Fisher's exact test. Categorical variables are presented as number and frequency, and continuous variables as means (standard deviations) or median (range). The Mantel–Haenszel test for trend was used to evaluate the trend in vaccine coverage from 2014 to 2018. The effect of the *pbp1b*A641C mutation on meningitis was estimated using a mixed-effects logistic regression model as described elsewhere (*10*). All statistical analyses were performed using IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA) or Stata software version 16 (StataCorp LLC, College Station, TX, USA). Statistical significance was set at $p < 0.05$.

Declarations

Ethics Statement

This study was reviewed and approved by the Ethics Committee of NIID (approval no. 707) and was conducted according to the principles expressed in the Declaration of Helsinki. The requirement for informed consent was waived because the data do not contain any patient identifiers and samples were taken as part of standard patient care.

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Author contribution

B.C., K.T., H.F., K.O., conceived and designed the study, and prepared the manuscript. B.C. and Y.K. generated bacteriological data. H.W., Y.T., K. K., J.F., K.O., T.M., S.A., K.K, J.N., T.K., Y.S., R.S., M.F., T.S., and M.S. collected epidemiological data.

Competing interests

The authors declare no competing interests.

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Tables

Due to technical limitations, tables 1 to 5 pptx are only available as a download in the Supplemental Files section.

Figures

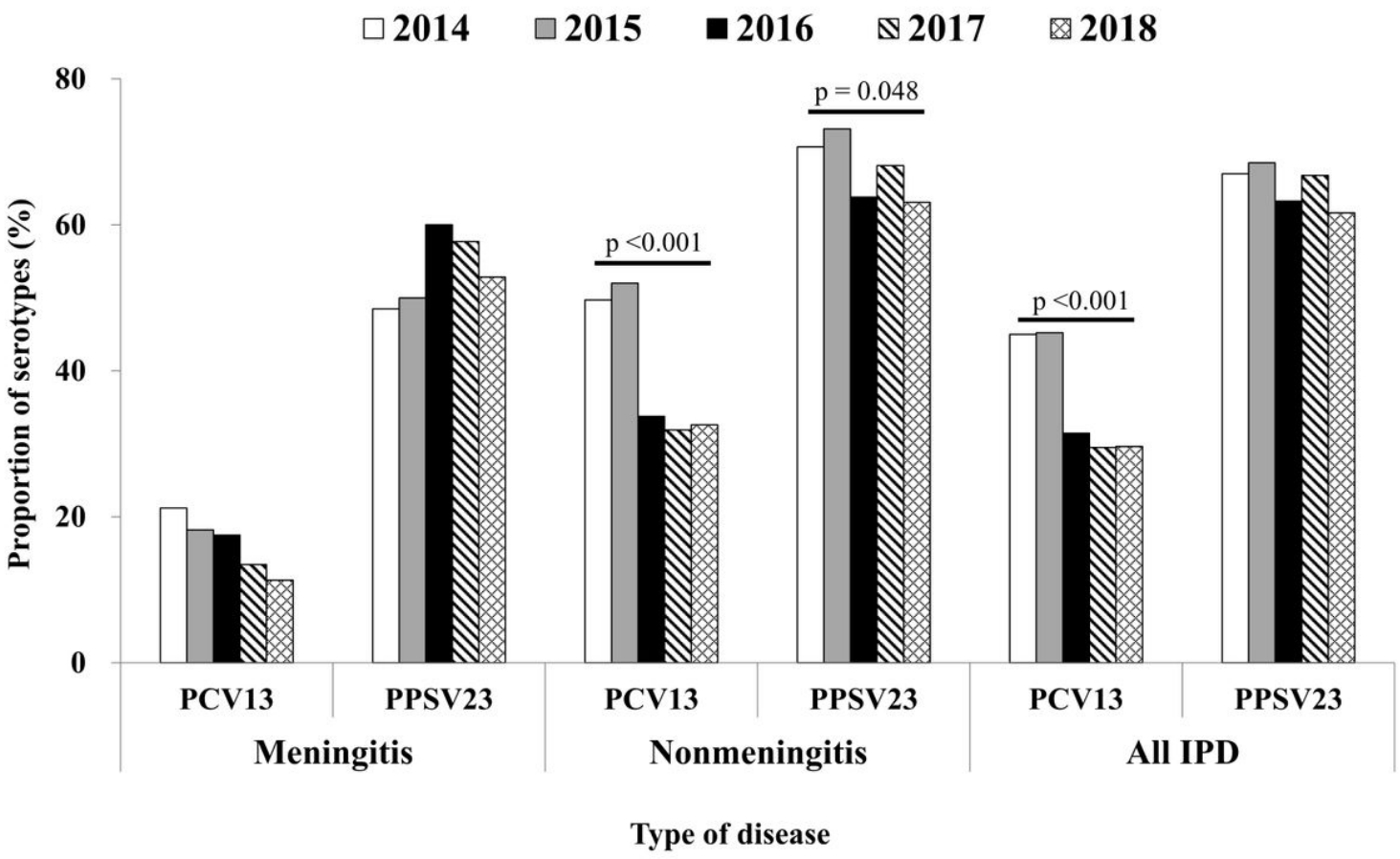

Figure 1

Percentage of vaccine-covered serotypes in pneumococcal isolates from 1,480 adult patients with invasive pneumococcal disease in Japan between 2014 and 2018, stratified by year and disease type. PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryinformation.pdf
- Table1.pptx
- Table2.pptx
- Table3.pptx
- Table4.pptx
- Table5.pptx