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The incidence of pediatric invasive *Haemophilus influenzae* and pneumococcal disease in Chiba prefecture, Japan before and after the introduction of conjugate vaccines

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ABSTRACT

The *Haemophilus influenzae* type b (Hib) vaccine and the heptavalent pneumococcal conjugate vaccine (PCV7) were introduced in Japan in 2008 and 2010, respectively. In 2011, immunization with these two vaccines was encouraged throughout Japan through a governmental program. Children treated in Chiba prefecture for culture-proven invasive *H. influenzae* disease (IHiD) and invasive *Streptococcus pneumoniae* disease (IPD) were identified in a prefectural surveillance study from 2008 to 2013. The incidence rate ratio (IRR) and its confidence interval (CI) were calculated to compare the 3 years before and after governmental financial support for vaccination. The average number of IHiD and IPD cases among children <5 years of age in 2011–2013 decreased 84% (IRR: 0.16, 95% CI: 0.09–0.26, $p < 0.0001$) and 51% (IRR: 0.49, 95% CI: 0.37–0.63, $p < 0.0001$) compared with those occurring in 2008–2010. The most common non-PCV7 serotype encountered in 2011 and 2013 was 19A. After governmental subsidization of Hib and PCV7 vaccination, IHiD and IPD decreased in Chiba prefecture, Japan. Continuous surveillance is necessary to determine the effectiveness of these two vaccines and for detection of emerging invasive serotypes.

1. Introduction

Haemophilus influenzae (*H. influenzae*) and *Streptococcus pneumoniae* (*S. pneumoniae*) are major causes of serious invasive infection, resulting in high mortality and morbidity in children due to meningitis, septicemia and pneumonia. Over the past decades, the incidence of serious infections due to strains of *H. influenzae* and *S. pneumoniae* having reduced susceptibility to penicillin and broad-spectrum cephalosporins has been steadily increasing in Japan [1,2]. The emergence of these strains has made the selection of antibiotics for treatment more difficult. The introduction of *H. influenzae* type b (Hib) conjugate vaccine and heptavalent pneumococcal conjugate vaccine (PCV7) has dramatically decreased the incidence of invasive Hib and invasive pneumococcal disease (IPD), respectively, all over the world [3–7]. However, in the United States and some other countries, surveillance studies following the introduction of PCV7 have demonstrated an increased prevalence of IPD caused by non-PCV7 serotypes, such as 6A, 19A, 15A, and 35B, suggesting that non-vaccine serotypes are emerging and replacing the vaccine serotypes [8–11]. These two vaccines have been included in the routine immunization program in Japan since April 2013, and the 13-valent pneumococcal conjugate vaccine (PCV13) was introduced in November 2013.

The targeted age group for both Hib conjugate and pneumococcal conjugate vaccination is children <5 years of age. The standard Japanese vaccination schedule for Hib conjugate vaccine consists of 3 doses, one administered at each of the ages of 2, 3, and 4 months, and then a booster at the age of 12–18 months. The standard Japanese vaccination schedule for PCV7 contains 3 doses, at

Abbreviations: Hib, *Haemophilus influenzae* type b; PCV7, heptavalent pneumococcal conjugate vaccine; IPD, invasive pneumococcal disease; PCV13, 13-valent pneumococcal conjugate vaccine; IHiD, invasive *Haemophilus influenzae* disease; IRR, incidence rate ratio; CI, confidence interval; NTHi, non-typeable *Haemophilus influenzae*; ST, sequence type.

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Table 1
Number of cases of invasive *Haemophilus influenzae* disease, by year.

	2008	2009	2010	2011	2012	2013	Total
Meningitis	23	18	29	7	4	0	81
Pneumonia	4	6	7	3	1	0	21
Bacteremia without focus	5	3	7	2	2	0	19
Cellulitis	2	1	3	0	0	1	7
Arthritis	2	3	1	0	0	0	6
Epiglottitis	0	1	1	1	0	0	3
Others	2	0	0	1	0	1	4
Total	38	32	48	14	7	2	141
Baseline population[a]	267,191	268.011	268,031	268,670	262,986	256,961	
Incidence[b] (95% CI)	13.5(9.4–18.7)	11.2(7.6–16.0)	16.8(12.3–22.5)	4.1(2.0–7.3)	1.9(0.6–4.4)	0.4(0.1–2.8)	

CI, confidence interval.
[a] Population <5 years of age.
[b] Cases/100,000 population <5 years of age.

the ages of 2, 3, and 4 months, and then a booster at the age of 12–15 months. After the Hib conjugate and PCV7 vaccines were included in the routine immunization program, these two vaccines were strongly recommended by the Vaccination Law and were given free of charge to all children <5 years of age in Japan.

Accurate, up-to-date information on the incidence of invasive *H. influenzae* diseases (IHiD) and IPD is fundamental for estimating vaccine efficacy and for formulating country-appropriate decision-making regarding management of Hib and pneumococcal conjugate vaccination. However, there is little information regarding the incidence of IHiD and IPD in children in Japan. The purpose of this study was to clarify the incidence of IHiD and IPD in children in the prefecture of Chiba, Japan, using population-based surveillance before and after the introduction of the Hib and pneumococcal conjugate vaccines.

2. Materials and methods

To determine the precise incidence of IHiD and IPD in Chiba prefecture, we conducted a survey during the 2008–2013 time period. Chiba prefecture is one of 47 prefectures in Japan, and is located in the middle of the country. The population in Chiba prefecture is about 6 million, which represents about 5% of the population of Japan. The population of children less than 5 years of age in Chiba prefecture in 2008, 2009, 2010, 2011, 2012, and 2013 was 267,191, 268,011, 268,031, 268,670, 262,986, and 256,961, respectively. We implemented a reporting system for IHiD and IPD in all 58 hospitals in Chiba prefecture, and 11 hospitals located in the surrounding area, that have pediatric wards, to determine the precise population-based incidence in Chiba prefecture. This active surveillance was conducted from 1 January 2008 through 31 December 2013. If the doctors in the targeted hospital treated children aged <16 years who lived in Chiba prefecture for IHiD or IPD, they used standardized case report forms to record patient and laboratory information, and then sent the case report form to Chiba University Hospital by fax or In addition to the reporting system, a written questionnaire was sent to enrolled hospitals twice a year for the identification of unreported cases. The case report form and the questionnaire included the clinical diagnosis, patient's age, underlying disease, vaccination history, treatment and prognosis. Invasive disease was defined as any disease where *S. pneumoniae* and *H. influenzae* was identified in normally sterile body fluids such as blood, cerebrospinal fluid, bone aspirate, or synovial fluid. All recorded pneumonia, cellulitis, and epiglottitis cases were confirmed by the presence of *S. pnemoniae* or *H. influenzae* in blood culture. If the isolated strains had been stocked in the hospital, the strains were sent to Chiba University where serotypes were analyzed. Serotypes of *H. influenzae* isolates were identified by coagulation using antiserum purchased from Denka Seiken (Tokyo, Japan). Serotypes of pneumococcal isolates were identified by the capsular quelling reaction, using antiserum purchased from the Statens Serum Institut (Copenhagen, Denmark). All collected strains were sent to the National Institute of Infectious Diseases, where serotypes were confirmed using the same methods. All statistical analyses were performed by using SAS software version 9.3 (SAS Institute, Cary, NC, USA) and the *R* statistical program, version 2.13. The total incidence rate for children within the 0–4 year age group was calculated for the period 2008–2013, as the number of those with IHiD or IPD per 100,000 in the Chiba prefecture. To compare disease ratios in 2008–2010 with those in 2011–2013, the incidence rate ratio (IRR) and its 95% confidence interval (CI) were calculated. This study was approved by Chiba University Ethics Committee Number 666. Informed consent for collection and use of patient information and specimens was obtained from each parent/guardian.

3. Results

3.1. IHiD

During the 6 years of this study, 141 patients were diagnosed with IHiD. Among these, 81 had meningitis, 21 had pneumonia, and 19 had bacteremia without a focus (Table 1). The highest annual incidence rate of IHiD and *H. influenzae* meningitis among children <5 years of age during the study period both occurred in 2010, and were 16.8 and 10.4 per 100,000, respectively, whereas the corresponding lowest annual incidence rates both occurred in 2013, and were 0.4 and 0, respectively (Fig. 1). The ages of onset of IHiD were available for all 141 patients: 53 (37.6%) were in the 0 year old subgroup, 44 (31.2%) in the 1 year old subgroup, 31 (22.0%) in the 2–4 year old subgroup, and 13 (9.2%) in the 5 years or older subgroup. Males constituted 50% of the subjects (70/141). At least one underlying condition was documented in 14 (9.9%) of the 141 IHiD patients. These included congenital anomaly/syndrome ($n = 5$), low birth weight infant ($n = 4$), malignancy ($n = 3$) and others ($n = 2$). Among IHiD cases at age 5 and over, 61.5% had underlying disease. Of the 141 study patients, 8 patients (5.7%) developed permanent neurological complications; 7 of the 8 patients with neurological sequelae had meningitis and one patient had deep cervical abscess. The Hib vaccination rates, including at least one shot, among cases of IHiD in 2008, 2009, 2010, 2011, 2012, and 2013 were 0%, 0.3% (1/32), 4.2% (2/48), 0%, 28.6% (2/7), and 50.0% (1/2), respectively. The capsular type of isolated *H. influenzae* strains was found for 115 strains (115/141; 81.6%). Of these 115 strains, 107 (93.0%) were Hib strains and 8 (7.0%) were non-typeable *H. influenzae* (NTHi). Yearly changes in Hib coverage in 2008, 2009, 2010, 2011, 2012, and 2013 were 100%, 100%, 89.7%, 92.3%, 66.7%, and 50.0%, respectively (Fig. 2). Among 5 strains isolated from the patients who received at least one shot of Hib conjugate vaccine, 3 strains were Hib and 2 strains were NTHi. All vaccinated patients were <2 years of age.