院)，信太　知(江別市立病院)，依田弥奈子，橋本　真(市立函館病院)，脇口定衛，飯塚　進，小籏菜穂，宮　卓也，大橋宏史(天使病院)，小杉山清隆，山崎健史，植木将弘，森岡圭太，上田泰弘(日鋼記念病院)，佐藤泰征，盛一享徳(KKR札幌医療センター)，久保憲昭，小原敏生，橋本　真(苫小牧市立病院)，鈴木秀久，兼次洋介(王子総合病院)，立花幸晃(網走厚生病院)，坂田　宏(旭川厚生病院)，藤保洋明(富良野協会病院)，石岡　透(遠軽厚生病院)，石倉亜矢子，寺下友佳代(函館中央病院)，佐藤俊哉(岩見沢市立総合病院)，大柳玲嬉，渡辺年香(北海道子ども総合医療・療育センター)，森田啓介(旭川赤十字病院)，東館義仁(札幌社会保険総合病院)，菊池成徳(砂川市立病院)，東海林黎吉(市立室蘭総合病院)，黒岩由紀，松田麻里，星野恵美子(NTT東日本札幌病院)，平木雅久(滝川市立病院)，竹田貴弘(市立稚内病院)

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日本小児科学会の定める利益相反に関する開示事項はありません．

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Epidemiology of Bacterial Meningitis in Childhood before and after the Introduction of Conjugate Vaccines in Hokkaido, the Northernmost Main Island of Japan

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We started in 2007 the surveillance of bacterial meningitis among children in Hokkaido which is geographically isolated from Mainland Honshu. During 5 years from 2007 through 2011, designated as the pre-vaccination period during which the vaccination rate was estimated to be under 30% among children under 7 months of age, 60 cases (12 a year) of *H. Influenzae* meningitis and 20 cases (4 a year) of *Streptococcus Pneumoniae* meningitis were reported by pediatric doctors in 35 hospitals, whereas in 2012 designated as the post-vaccine period, during which the vaccination rate was estimated over 90% among children under 7 months of age, none of *H. Influenzae* meningitis and 1 case of *Streptococcus Pneumoniae* meningitis was reported from 1 hospital. The reason for the dramatic decrease of meningitis cases due to the main two pathogens will be by the introduction of an official vaccination program "the *Provisional Special Fund for the Urgent Promotion of Vaccination*" from November 2010 which encourages the vaccination of Hib and PCV7 for children under 5 years throughout Japan.

Recently meningitis patients due to the serotype 19A and 6C of *Streptococcus Pneumoniae* were reported in Hokkaido, further serotype surveillance should be continued and the introduction of PCV10 and/or PCV13 should be expected in Japan.

Immunogenicity and Safety of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants in Japan

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Background: A 13-valent pneumococcal conjugate vaccine (PCV13) containing 6 additional serotypes not included in the 7-valent PCV has been developed to broaden protection against *Streptococcus pneumoniae*, which is responsible for over 500,000 deaths annually worldwide in children <5 years of age. This study in Japanese infants evaluated the immunogenicity and safety of PCV13 given subcutaneously, the standard route for infant vaccination in Japan.

Methods: This phase 3, single-arm, open-label study was conducted at 25 sites. Subjects received PCV13 as a 3-dose infant series and a toddler dose. Parents/legal guardians recorded local reactions and systemic events after each vaccination. The proportion of subjects with serotype-specific antipneumococcal polysaccharide immunoglobulin (Ig)G antibody concentrations ≥0.35 μg/mL was calculated before and 1 month after the infant series and toddler dose.

Results: A total of 193 subjects enrolled. The proportion of subjects achieving pneumococcal IgG antibody concentrations ≥0.35 μg/mL was ≥97.2% for all 13 pneumococcal serotypes 1 month after the infant series and 98.9–100% after the toddler dose. IgG geometric mean concentrations were 2.57–14.69 μg/mL after the infant series and 2.06–16.33 μg/mL after the toddler dose. IgG geometric mean concentrations increased from pre- to posttoddler dose by ≥2.8-fold, demonstrating a booster effect. Local reactions and fever were generally mild or moderate in severity.

Conclusions: PCV13 was immunogenic for all serotypes and had a favorable safety profile when administered subcutaneously to Japanese infants. PCV13 should offer broader serotype protection than 7-valent PCV in preventing pneumococcal disease in Japanese children.

Key Words: pneumococcal vaccine, Japan, immunogenicity, safety, pediatric

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Streptococcus pneumoniae causes serious invasive and mucosal infections and is responsible for approximately 541,000 deaths annually worldwide in children <5 years of age.[1] In Japan, *S. pneumoniae* caused approximately 15% of cases of bacterial meningitis in children before introduction of the 7-valent pneumococcal conjugate vaccine (PCV7).[2] PCV7 has demonstrated efficacy[3–6] and effectiveness[7–9] against pneumococcal diseases outside Japan. To broaden protection, a 13-valent PCV (PCV13), which contains 6 additional serotypes (1, 3, 5, 6A, 7F and 19A) in addition to the 7 serotypes in common with PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F), has been developed.

Serotypes included in PCV13 are found in approximately 80–94% of isolates causing invasive pneumococcal disease (IPD) and approximately 56–92% of antibiotic-nonsusceptible isolates from children in Japan.[10–13] Of note, PCV13 serotype 19A was isolated in 6.3–12.5% of isolates from children with IPD before the introduction of PCV7 in Japan.[10,12] Studies in Europe, North America and Asia have demonstrated that PCV13 elicits similar immune responses to the 7 common serotypes as those elicited by PCV7, and substantially greater immune responses to the 6 additional serotypes.[14–22] In addition, early reports suggest that PCV13 is effective in reducing incidence of PCV13 serotype disease and nasopharyngeal carriage.[23,24] This study in Japanese infants evaluated the immunogenicity and safety of PCV13 given subcutaneously, the standard route for infant vaccination in Japan.

METHODS

Study Design and Population

This phase 3, single-arm, open-label study was conducted at 25 sites in Japan in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the ethical principles that have their origins in the Declaration of Helsinki. Subjects were healthy infants aged 2–6 months at enrollment. Exclusion criteria included previous vaccination with pneumococcal vaccine, contraindications to any vaccine-related component, immune deficiency or suppression, history of IPD or serious disorder, receipt of blood products and participation in another investigational or interventional trial. Subjects received PCV13 as a 3-dose infant series and a toddler dose. Dose 1 of the infant series was administered between ages 2 and 6 months; dose 2 and dose 3, ≥28 days after dose 1 and dose 2, respectively, but before age 12 months. The toddler dose was administered between ages 12 and 15 months, but ≥60 days after dose 3.

Vaccines Administered

PCV13 contains the polysaccharides from the 7 serotypes included in PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F) plus 6 additional serotypes (1, 3, 5, 6A, 7F and 19A), each covalently conjugated to the carrier protein cross-reactive material 197, a nontoxic variant of diphtheria toxin. The vaccine was formulated to contain 2.2 μg of each polysaccharide, except for 4.4 μg of serotype 6B, per 0.5-mL dose. The final formulation contained 5 mM succinate buffer, with 0.125 mg of aluminum as aluminum phosphate per 0.5-mL dose, and polysorbate 80 at 0.02% as an excipient. PCV13 was

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administered subcutaneously in either arm. No concomitantly administered vaccines were permitted, consistent with the standard of care for infant/childhood immunizations in Japan at the time of the study. Live vaccines could be given ≥28 days before PCV13, and nonlive vaccines could be given ≥7 days before PCV13; live or nonlive vaccines could be given ≥7 days after PCV13.

Immunogenicity Assessment

Blood samples for immunogenicity assessment were obtained before and 1 month after the infant series and toddler dose. Serotype-specific antipneumococcal IgG concentrations were measured using a standardized enzyme-linked immunosorbent assay to measure the concentration of antipolysaccharide binding IgG antibodies.[25–28] The double-absorption enzyme-linked immunosorbent assay used a cell wall extract containing cell wall polysaccharide plus serotype 22F capsular polysaccharide containing cell wall polysaccharide-2.

Safety Assessment

Parents/legal guardians recorded in an electronic diary the subject's local reactions (redness, swelling and tenderness), systemic events and the use of antipyretic medication for 7 days after each vaccination. Parents/legal guardians used a caliper to measure redness and swelling in units of 1 to >14, with each caliper unit representing 0.5 cm. Tenderness was recorded as none, present or interfered with limb movement. Systemic events included fever, decreased appetite, irritability, increased sleep, decreased sleep and hives (urticaria). Axillary temperature was measured daily at bedtime or any time fever (≥37.5°C) was suspected; the highest temperature each day was to be recorded. Other adverse events (AEs) were also collected at clinic visits, and a paper diary was provided as a memory aid to parents/legal guardians to record information between visits. AEs were collected during the study from the signing of the informed consent form to 1 month postinfant series, and from the toddler dose to the last study visit, 1 month posttoddler dose. Serious AEs (SAEs) were collected throughout the study to the last study visit.

Statistical Analysis Methods

The proportions of subjects with serotype-specific antipneumococcal polysaccharide IgG antibody concentrations ≥0.35 μg/mL, the reference antibody concentration for assessment of vaccine efficacy against IPD defined by the World Health Organization,[29–31] were calculated before and 1 month after the infant series (primary endpoint) and toddler dose (secondary endpoint). Exact, unconditional, 2-sided 95% confidence intervals (CIs) on the proportion were calculated. Serotype-specific IgG geometric mean antibody concentrations (GMCs) were assessed before and 1 month after the infant series and the toddler dose (secondary endpoints). Two-sided, 95% CIs were constructed. Geometric mean fold rises were calculated for each serotype based on data obtained before and after the toddler dose.

The evaluable immunogenicity population included all subjects who received all study vaccinations, had blood drawn within the protocol-specified time frames, had ≥1 valid and determinate assay result and had no major protocol violations. All subjects who received ≥1 dose of PCV13 were included in the safety analysis, which included incidences of local reactions, systemic events and AEs summarized separately for each dose of study vaccine.

RESULTS

Subject Disposition and Demographics

A total of 193 subjects were enrolled in the study (Fig. 1). Of all subjects, 51.8% were male, all were Japanese, and mean age at enrollment was 3.7 months.

Immunogenicity

Infant Series

Before the infant dose, the proportion of subjects with pneumococcal antibody concentrations ≥0.35 μg/mL was relatively low, ranging from 1.1% (serotype 4) to 50.6% (serotype 19A). One month after the infant series, the proportion of subjects achieving pneumococcal antibody concentrations ≥0.35 μg/mL was ≥97.2% for all 13 pneumococcal serotypes (Tables 1 and 2). IgG GMCs were 0.03 μg/mL (serotype 4) to 0.35 μg/mL (serotype 19A) before the infant dose and increased substantially to 2.57 μg/mL (serotype 23F) to 14.69 μg/mL (serotype 14) 1 month after the infant series (Tables 1 and 2).

Toddler Dose

Before the toddler dose, the proportion of subjects with pneumococcal antibody concentrations ≥0.35 μg/mL ranged from 79.2% (serotype 3) to 100% (serotypes 14 and 7F). One month after the toddler dose, the proportion of subjects achieving pneumococcal antibody concentrations ≥0.35 μg/mL was ≥98.9% for all 13 pneumococcal serotypes (Tables 1 and 2). IgG GMCs declined by the time of the toddler dose, but increased substantially from pre- to posttoddler dose for all serotypes. IgG GMCs pretoddler dose ranged from 0.73 μg/mL (serotype 3) to 5.25 μg/mL (serotype 14) and from 2.06 μg/mL (serotype 3) to 16.33 μg/mL

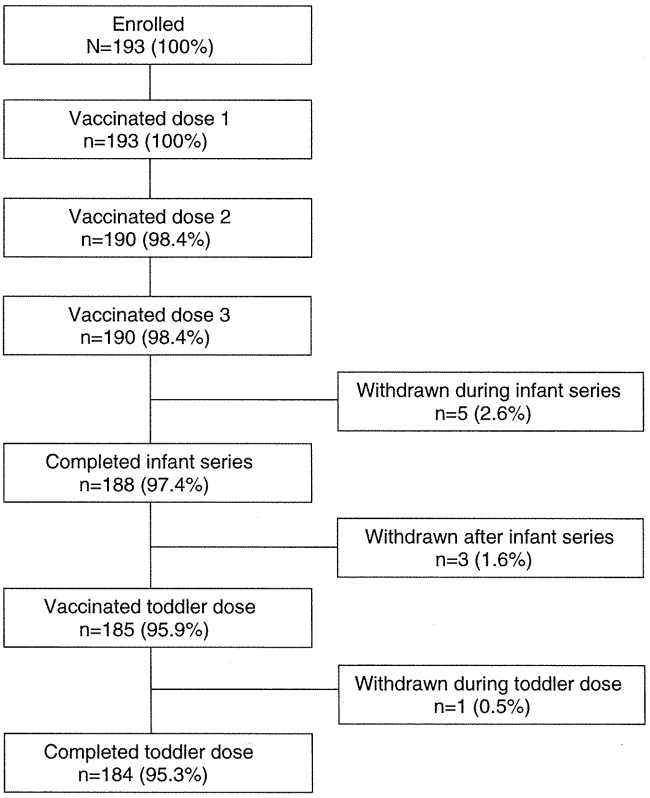

FIGURE 1. Subject disposition.

TABLE 1. Immune Responses to PVC13 Before Vaccination, 1 Month After the Infant Series, Before the Toddler Dose and 1 Month After the Toddler Dose (Evaluable Immunogenicity Population), 7 Serotypes Common to PCV7 and PCV13

	Serotype						
	4	6B	9V	14	18C	19F	23F
Before infant series							
Proportion of subjects with IgG concentration ≥0.35 μg/mL (95% CI)*	1.1 (0.1–4.1)	31.2 (24.4–38.7)	5.1 (2.4–9.5)	30.7 (24.0–38.1)	4.0 (1.6–8.1)	13.2 (8.6–19.2)	19.9 (14.3–26.6)
IgG GMC (μg/mL) (95% CI)†	0.03 (0.02–0.03)	0.22 (0.18–0.25)	0.08 (0.07–0.09)	0.17 (0.14–0.21)	0.06 (0.05–0.07)	0.14 (0.12–0.16)	0.12 (0.10–0.14)
Postinfant series							
Proportion of subjects achieving IgG concentration ≥0.35 μg/mL (95% CI)*	100 (97.9–100)	98.3 (95.1–99.6)	100 (97.9–100)	100 (97.9–100)	100 (97.9–100)	97.2 (93.5–99.1)	97.7 (94.3–99.4)
IgG GMC (μg/mL) (95% CI)†	6.76 (6.02–7.59)	4.77 (4.07–5.59)	3.39 (3.03–3.78)	14.69 (13.26–16.26)	3.68 (3.27–4.14)	5.71 (4.90–6.65)	2.57 (2.21–3.00)
Pretoddler dose							
Proportion of subjects with IgG concentration ≥0.35 μg/mL (95% CI)*	97.8 (94.3–99.4)	98.9 (96.0–99.9)	94.9 (90.6–97.7)	100 (97.9–100)	89.3 (83.8–93.4)	97.8 (94.3–99.4)	83.0 (76.6–88.2)
IgG GMC (μg/mL) (95% CI)†	1.68 (1.48–1.90)	2.53 (2.23–2.86)	1.09 (0.97–1.22)	5.25 (4.62–5.97)	0.92 (0.81–1.05)	2.28 (1.95–2.67)	0.90 (0.77–1.05)
Posttoddler dose							
Proportion of subjects achieving IgG concentration ≥0.35 μg/mL (95% CI)*	100 (97.9–100)	100 (97.9–100)	100 (97.9–100)	100 (97.9–100)	100 (97.9–100)	98.9 (96.0–100)	98.9 (96.0–100)
IgG GMC (μg/mL) (95% CI)†	9.70 (8.43–11.17)	14.61 (12.52–17.05)	4.49 (4.00–5.06)	16.33 (14.49–18.41)	6.09 (5.34–6.95)	12.2 (10.37–14.25)	6.55 (5.53–7.75)
IgG GMFR‡ (95% CI)†	5.79 (5.07–6.61)	5.72 (5.01–6.52)	4.13 (3.72–4.60)	3.11 (2.71–3.57)	6.60 (5.83–7.47)	5.34 (4.63–6.17)	7.48 (6.56–8.54)

*Exact 2-sided 95% CIs for % responders are based on the observed proportion of subjects.
†CIs are back transformations of a CI based on the Student *t* distribution for the mean logarithm of the concentrations or the mean fold rises.
‡GMFRs were calculated using all subjects with available data from both the pretoddler dose and posttoddler dose blood draws.
GMFR indicates geometric mean fold rise.

(serotype 14) 1 month after the toddler dose (Tables 1 and 2), with geometric mean fold rises (pre- to posttoddler) ranging from 2.83 (serotype 3) to 7.48 (serotype 23F) (Tables 1 and 2). In addition, IgG GMCs were higher after the toddler dose compared with those after the infant series for 12 serotypes; 95% CIs did not overlap between postinfant series and posttoddler dose for 11 of these 12 serotypes, with the exception of serotype 14. A slight but statistically lower IgG GMC was seen for serotype 3 after the toddler dose compared with results after the infant dose, but the proportion of subjects with pneumococcal antibody concentrations ≥0.35 μg/mL was not statistically different between the postinfant series and posttoddler dose.

Safety

Local reactions were generally mild or moderate in severity (Table 3). The most commonly reported local reactions were swelling and redness (Table 3). The most commonly reported systemic events were irritability and increased sleep (Table 4). One subject reported severe fever (>40°C) after dose 2. AEs were generally consistent with childhood illnesses and conditions common in this age group. The most common category of AEs was infections and infestations. AEs considered related to study vaccine were generally injection site reactions, which may be related to the subcutaneous route of administration of vaccine. During the infant series, the most common related AEs were redness (10.9%), swelling (8.3%) and diarrhea (5.2%). After the toddler dose, the most common related AEs were injection site redness (9.7%) and fever (2.2%). A total of 30 SAEs were reported for 22 subjects; none was considered related to study vaccine. No subjects died during the study. Three subjects withdrew from the study due to AEs. One subject who withdrew experienced moderate injection site swelling and erythema after each infant dose and mild fever after doses 2 and 3; these AEs were considered related to study vaccine. Two subjects withdrew due to febrile convulsions due to viral exanthema/exanthema subitum (n = 1) and upper respiratory tract infection (n = 1), which occurred 96 and 113 days, respectively, after vaccination; these SAEs were considered not related to study vaccine.

DISCUSSION

Vaccination with PCV13 elicited strong antipneumococcal IgG responses in Japanese children to all 13 pneumococcal serotypes when measured 1 month after the infant series and 1 month after the toddler dose. These responses were similar to those reported in studies of PCV13 in other Asian populations[16,21,22] and higher than those reported in other studies of PCV13 in countries outside Asia, including the United States,[15] Germany[14] and Canada.[20] The present Japanese study differed from the studies in the United States, Canada and Germany not only in the ethnicity of the subjects but also in aspects of study design, including older age range (up to age 6 months) at enrollment, longer interval between vaccine doses, no concomitant vaccines and subcutaneous administration.[14,15,20] Of note, the immune responses elicited to the PCV7 serotypes were comparable to those reported in studies in other Asian countries, in which children were vaccinated with PCV7 via intramuscular administration.[32–35] Subjects in these studies had generally higher levels of immune response to PCV7 than in studies of PCV7 in the United States[3,36] and Europe,[4,37] suggesting that responses to PCVs may generally be higher in Asian populations compared with European or North American populations, regardless of the route of administration.

Immune responses increased posttoddler dose compared with postinfant series for all serotypes except serotype 3, reflecting immunological memory. IgG GMCs for serotype 3 after the toddler dose and the infant series had nonoverlapping 95% CIs, but the

TABLE 2. Immune Responses to PVC13 Before Vaccination, 1 Month After the Infant Series, Before the Toddler Dose and 1 Month After the Toddler Dose (Evaluable Immunogenicity Population), 6 Additional Serotypes

	Serotype					
	1	3	5	6A	7F	19A
Before infant series						
Proportion of subjects with IgG concentration ≥0.35 μg/mL (95% CI)*	3.4 (1.3–7.3)	3.4 (1.3–7.3)	42.9 (35.4–50.5)	31.6 (24.8–39.1)	5.1 (2.4–9.5)	50.6 (42.9–58.2)
IgG GMC (μg/mL) (95% CI)†	0.05 (0.04–0.05)	0.06 (0.06–0.07)	0.30 (0.27–0.35)	0.24 (0.21–0.28)	0.07 (0.06–0.08)	0.35 (0.31–0.40)
Postinfant series						
Proportion of subjects achieving IgG concentration ≥0.35 μg/mL (95% CI)*	100 (97.9–100)	100 (97.9–100)	100 (97.9–100)	100 (97.9–100)	100 (97.9–100)	100 (97.9,100)
IgG GMC (μg/mL) (95% CI)†	5.11 (4.48–5.82)	2.87 (2.55–3.24)	3.85 (3.42–4.33)	3.77 (3.35–4.25)	5.78 (5.19–6.45)	6.97 (6.25–7.77)
Pretoddler dose						
Proportion of subjects with IgG concentration ≥0.35 μg/mL (95% CI)*	97.2 (93.6–99.1)	79.2 (72.5–84.9)	98.9 (96.0–99.9)	99.4 (96.9–100)	100 (97.9–100)	99.4 (96.9–100)
IgG GMC (μg/mL) (95% CI)†	1.54 (1.34–1.77)	0.73 (0.64–0.83)	2.11 (1.88–2.37)	2.21 (1.96–2.49)	2.27 (2.02–2.55)	3.16 (2.76–3.62)
Posttoddler dose						
Proportion of subjects achieving IgG concentration ≥0.35 μg/mL (95% CI)*	100 (97.9–100)	99.4 (96.9–100)	100 (97.9–100)	100 (97.9–100)	100 (97.9–100)	100 (97.9–100)
IgG GMC (μg/mL) (95% CI)†	9.85 (8.62–11.27)	2.06 (1.83–2.32)	7.31 (6.52–8.20)	11.03 (9.69–12.55)	8.31 (7.39–9.35)	15.97 (14.07–18.13)
IgG GMFR‡ (95% CI)†	6.41 (5.62–7.30)	2.83 (2.53–3.17)	3.46 (3.14–3.81)	4.99 (4.38–5.68)	3.66 (3.27–4.10)	5.05 (4.46–5.72)

*Exact 2-sided 95% CIs for % responders are based on the observed proportion of subjects.
†CIs are back transformations of a CI based on the Student *t* distribution for the mean logarithm of the concentrations or the mean fold rises.
‡GMFRs were calculated using all subjects with available data from both the pretoddler dose and posttoddler dose blood draws.
GMFR indicates geometric mean fold rise.

proportion of subjects with pneumococcal antibody concentrations ≥0.35 μg/mL was similar at both time points. Previous studies have also noted similar IgG GMC responses to serotype 3 elicited by PCV13 posttoddler dose compared with those postinfant series.[14,15] Importantly, responses to serotype 3 as measured by opsonophagocytic activity assays increased from postinfant series to posttoddler dose in both these studies, demonstrating a functional booster response.

Early effectiveness data for PCV13 have begun to be reported. During the first 15 months after introduction of PCV13 in England and Wales, there was a 50% reduction in the incidence of IPD cases caused by the additional serotypes in PCV13 (including the cross-reactive serotype 6C) in children <2 years of age.[23] The vaccine effectiveness of PCV13 against all PCV13 serotypes (including serotype 6C) was 78% (95% CI: −18 to 96) for children receiving 2 doses at <12 months of age and 73% (95% CI: 29–90) for children receiving 1 dose at ≥12 months of age; in addition, significant effectiveness of ≥1 dose of PCV13 was demonstrated against PCV13 serotypes 7F (vaccine effectiveness 76%; 95% CI: 21–93) and 19A (vaccine effectiveness 70%; 95% CI: 10–90).[23] Of note, effectiveness of PCV13 against serotype 3 has not yet been demonstrated. It is anticipated that additional studies will provide further information on PCV13 effectiveness in the United States, the United Kingdom and other regions of the world.

PCV13 was well tolerated by subjects in this study. The types of AEs reported were generally consistent with common childhood illnesses and conditions in this age group. In Japan, subcutaneous administration is the standard route for childhood immunization. Local site reactions, particularly redness and swelling, occurred

TABLE 3. Proportion of Subjects Reporting Local Reactions Within 7 Days of Each Dose of PCV13

	Infant Series			
% (n/N)	Dose 1	Dose 2	Dose 3	Toddler Dose
Tenderness				
Any	13.3 (22/165)	19.9 (31/156)	14.3 (21/147)	18.2 (26/143)
Significant*	0.6 (1/160)	0 (0/152)	0 (0/143)	0 (0/132)
Swelling				
Any	47.2 (83/176)	53.8 (93/173)	53.9 (89/165)	57.1 (93/163)
Mild†	46.0 (80/174)	49.1 (84/171)	50.3 (82/163)	44.2 (68/154)
Moderate†	14.4 (24/167)	28.7 (47/164)	29.3 (44/150)	36.4 (55/151)
Severe†	0 (0/160)	1.3 (2/153)	0.7 (1/143)	2.3 (3/132)
Redness				
Any	74.2 (138/186)	74.4 (134/180)	67.8 (116/171)	68.1 (113/166)
Mild†	68.3 (125/183)	64.8 (116/179)	55.6 (90/162)	53.8 (84/156)
Moderate†	24.7 (42/170)	43.5 (73/168)	38.9 (61/157)	40.6 (63/155)
Severe†	0 (0/160)	1.3 (2/153)	0.7 (1/143)	1.5 (2/132)

*Significant indicates present and interfered with limb movement.
†Mild, 0.5–2.0 cm; moderate, 2.5–7.0 cm; and severe, >7.0 cm.
n/N indicates number of subjects reporting the specific characteristic/number of subjects reporting "yes" for ≥1 day or "no" for all days.

TABLE 4. Proportion of Subjects With Systemic Events or Antipyretic Medication Use Within 7 Days of Each Dose of PCV13

Systemic Event or Medication Use, % (n/N)	Infant Series			Toddler Dose
	Dose 1	Dose 2	Dose 3	
Any fever (≥37.5°C)	32.9 (56/170)	33.1 (54/163)	40.3 (62/154)	50.7 (76/150)
Mild fever (≥38°C but ≤39°C)	6.7 (11/163)	12.2 (19/156)	10.3 (15/146)	20.4 (28/137)
Moderate fever (>39°C but ≤40°C)	1.2 (2/161)	2.6 (4/153)	2.8 (4/143)	5.3 (7/133)
Severe fever (>40°C)	0 (0/160)	0.7 (1/152)	0 (0/143)	0 (0/132)
Decreased appetite	11.7 (19/163)	16.5 (26/158)	9.7 (14/144)	18.1 (25/138)
Irritability	30.6 (52/170)	36.1 (60/166)	23.5 (35/149)	26.4 (37/140)
Increased sleep	40.6 (71/175)	29.4 (47/160)	22.2 (34/153)	24.5 (34/139)
Decreased sleep	21.3 (36/169)	23.1 (37/160)	15.9 (23/145)	12.3 (17/138)
Hives (urticaria)	1.3 (2/160)	1.3 (2/152)	0.7 (1/143)	0 (0/132)
Use of medication to treat symptoms	1.9 (3/160)	6.5 (10/153)	5.5 (8/145)	8.1 (11/135)
Use of medication to prevent symptoms	0.6 (1/160)	3.3 (5/153)	2.1 (3/144)	3.0 (4/134)
Any systemic event*	59.1 (107/181)	60.0 (105/175)	43.7 (69/158)	52.0 (79/152)

*Includes fever ≥38°C, decreased appetite, irritability, increased sleep, decreased sleep and hives (urticaria).
n/N indicates number of subjects reporting the specific characteristic/number of subjects reporting "yes" for ≥1 day or "no" for all days.

at somewhat higher rates in this study compared with studies that administered PCV13 via intramuscular injection.[14–16] In this study, 47.2–57.1% of subjects had any swelling and 68.1–74.4% had any redness at the injection site, compared with 7.9–44.0% and 15.4–54.4% of subjects, respectively, who received intramuscular injections in other studies.[14–16] Nevertheless, local reactions in this study were generally mild or moderate, consistent with other published studies.[14–16]

This was an open-label study that had only 1 treatment arm, so the data on immune response to PCV13 in this population were not directly compared with immune responses to PCV7. However, the substantial increase in responses following the infant series and toddler dose clearly demonstrate the immunogenicity of PCV13 in this population. PCV13 elicited robust immune responses, was well tolerated and had a favorable safety profile when administered subcutaneously to Japanese infants. PCV13 should offer broader serotype protection in preventing pneumococcal disease in Japanese children.

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POPULATION-BASED INCIDENCE OF INVASIVE *HAEMOPHILUS INFLUENZAE* AND PNEUMOCOCCAL DISEASES BEFORE THE INTRODUCTION OF VACCINES IN JAPAN

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Abstract: Before the introduction of vaccines, the incidence of bacterial meningitis among children aged 28 days to 5 years was 8.48, *Haemophilus influenzae* type-b meningitis was 5.65 and *Streptococcus pneumoniae* meningitis was 1.85 per 100,000 person-years in Hokkaido, Japan. The incidence of bacteremia caused by *S. pneumoniae* was 60.15 and *H. influenzae* was 18.80.

Key Words: Haemophilus influenzae type-b disease, pneumococcal disease, pneumococcal conjugate vaccine, Haemophilus influenzae type-b vaccine, Japan

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In August 2012, reports emerged that the Japanese government planned to add *Haemophilus influenzae* type-b (Hib) vaccine, 7-valent pneumococcal conjugate vaccine (PCV7), and human papillomavirus vaccine to the routine schedule in April 2013. Japan moved from its decades-old conservative vaccine policy toward the active vaccine policy. The milestone event was approval of the Hib vaccine in 2007, after nearly 10 years of discussions between the manufacturer and the Japanese government. Not long after the Hib vaccine was approved, PCV7 was approved in 2009, and human papillomavirus vaccines were approved in 2010 and 2011.

Japan is a relatively small, highly populated country with a universal healthcare system that allows all citizens to access any healthcare facility, regardless of place of residence. People often cross prefecture borders to visit and be admitted to hospitals located outside of their place of residence. In addition to these facts, Japan has no centralized disease database; therefore, it is very difficult to obtain the population-based incidence data that serve as the basis for vaccine introduction. Our study area Hokkaido Prefecture is an island, thus one of very few places in Japan where population-based studies are possible.

METHODS

We conducted a comprehensive prospective study of invasive bacterial diseases among children aged 28 days to 5 years who were admitted to hospitals in Hokkaido Prefecture. All hospitals in the study area with a pediatric admission facility participated in the study. Only children whose blood or cerebrospinal fluid culture was positive and who legally resided in the study area were included in the study. Children clinically diagnosed with meningitis or bacteremia but who had negative culture results were excluded, irrespective of prior antibiotic use. Polymerase chain reaction diagnosis was available for culture-negative cases.

The study of bacterial meningitis throughout Hokkaido Prefecture began on January 1, 2007, after the institutional review boards of all 64 participating institutions had approved the protocol. Doctors were asked to immediately ship all bacteria cultured from cerebrospinal fluid to Kitasato University for serotyping using Transystem transport swabs (Copan Italia S.p.A, Brescia, Italy), which allow for maintenance of bacterial viability at room temperature. Between January 1, 2008, and December 31, 2010, we conducted a study of bacteremia in Eastern Hokkaido. We selected this area because it is geographically isolated from the rest of the prefecture by the Tokachi-Taisetsu Mountains, and therefore, the data remain population-based. *Streptococcus pneumoniae* specimens were preserved frozen in Microbank containers (Pro-Lab Diagnostics, Richmond Hills, ON, Canada) and shipped periodically to the Nagasaki University Institute of Tropical Medicine for serotyping. The bacteremia study protocol was approved by the Clinical Study Review Board at the Graduate School of Hokkaido University School of Medicine on December 21, 2007. The meningitis/bacteremia target populations were 206,910/35,244 in 2008, 204,247/35,035 in 2009 and 203,366/36,117 in 2010.

RESULTS

Meningitis

There were 87 admissions for bacterial meningitis among children aged 28 days to 5 years between January 1, 2007, and December 31, 2011, across Hokkaido Prefecture. Of these 87 cases, 59 cases were caused by *H. influenzae* (Hi) and 19 cases by *S. pneumoniae*. The calculated incidence of bacterial meningitis was 8.48, Hib meningitis was 5.65 and pneumococcal meningitis was 1.85 per 100,000 person-years in Hokkaido Prefecture. Fifteen of the 19 pneumococcal strains were serotyped. Reported serotypes were 6B (5), 23F (3), 19F (2), 14 (2), 6C (2) and 19A (1). The overall serotype coverage of PCV7 was 80% and PCV13 was 87%.

Bacteremia

Between 2008 and 2010, 101 admissions for invasive bacterial diseases were reported in Eastern Hokkaido. There were 92 cases of bacteremia and 11 cases of bacterial meningitis; 2 cases of meningitis occurred with bacteremia. *S. pneumoniae* infection accounted for 70% (64 cases), whereas Hi infection accounted for 22% (21 cases). Before introduction of the Hib vaccine and PCV7, the average annual incidence per 100,000 children aged 28 days to 5 years was 95.87 for invasive bacterial disease, 87.41 for bacteremia and 10.34 for meningitis in Eastern Hokkaido. The average incidence of bacteremia by pathogen was 60.15 (*S. pneumoniae*) and 18.80 (Hi). We serotyped 45 of 64 *S. pneumoniae* strains during the study period. Serotypes identified were 23F (12), 6A (10), 6B (8), 14 (5), 9A (3), 19A (2), 19F (1), 22F (1), 23A (1), 28A (1) and 9L (1). The average annual serotype coverage of PCV7 for bacteremia was 58% and PCV13 for bacteremia was 84%. Serotypes included only in PCV13 accounted for 26% (12/45) of all strains serotyped.

DISCUSSION

We presented the first population-based incidence data of vaccine preventable invasive bacterial diseases in Japan from a study conducted on the island of Hokkaido in this article. Before vaccines were introduced, the incidence of invasive Hi diseases in children <5 years old in Hokkaido Prefecture was 23, comparable with that in Europe (France: 21/100,000; Spain: 12/100,000),[1,2] where data primarily reflect hospital admissions. In contrast, the incidence of invasive pneumococcal diseases in Hokkaido was 63, comparable with that in the United States (54.7/100,000).[3] It is said that despite a similar socioeconomic status, the incidence is much

TABLE 1. Incidence of Invasive Bacterial Diseases and Serotype Coverage of PCV in Hokkaido and Okinawa Prefectures Before Vaccines Introduction (2008 to 2010)

	2008		2009		2010	
	Hokkaido	Okinawa	Hokkaido	Okinawa	Hokkaido	Okinawa
Incidence (/100,000)						
Meningitis						
All-cause	8.22	11.0	9.30	14.67	7.87	15.79*
Streptococcus pneumoniae	0.97	4.89	1.96	7.33	1.97	4.86
Hib	5.80	4.89	6.36	4.89	5.90	8.50
Bacteremia						
All-cause	113.49	N/A	85.63	N/A	60.91	N/A
S. pneumoniae	65.26	97.80	57.09	80.68	58.14	89.86
Hib/Hi	36.89	13.44	17.13	23.22	2.77	12.14
Invasive pneumococcal disease	71.06	102.69	59.05	88.01	60.11	97.42
Invasive Hib diseases	42.69	18.33	17.78	40.11	8.67	20.6
PCV serotype coverage for invasive pneumococcal disease (%)						
PCV7	44	65	82	82	58	76
PCV13	78	78	82	92	94	92
Population <5 yr (Eastern Hokkaido)	206,910 (35,244)	N/A	204,247 (35,035)	81,798	203,366 (36,117)	82,353

The PCV serotype coverage for Hokkaido is based on the data from Eastern Hokkaido.

Population data are based on the annual national census.

PCV coverage for Okinawa was modified from the data in the reports referred. According to the reports, as of the end of 2010, the vaccination coverage of both Hib vaccine and PCV7 in Okinawa remained very low.

*Data not available from the original report. Calculation was based on the number of cases shown in the 2011 report per population <5 years old.

N/A indicates not available.

higher in the United States than in Europe, presumably due to differences in blood culture practice.

To our knowledge, Sakata[4,5] conducted the only other population-based studies in Japan, prospectively estimating the incidence of bacterial meningitis among children <5 years old at 6.3/100,000 in 1993 to 2005 and retrospectively estimating the incidence of pneumococcal bacteremia at 30.95 in 1997 to 2004 in Hokkaido. Our estimated incidence in Hokkaido was almost double that of Sakata.

Recently, a population-based study using the same protocol used in our study was conducted in Okinawa Prefecture. Okinawa and Hokkaido are the only island prefectures in Japan. Okinawa Prefecture is subtropical islands situated at the southernmost end of the Japanese archipelago, whereas northernmost Hokkaido is subarctic. The rest of Japan is temperate. Despite some climatic and cultural differences, the socioeconomic status of both prefectures is similar to that of the rest of Japan. Compared with Hokkaido, the incidence of pneumococcal diseases in Okinawa was 2.5–5 times higher for meningitis and 1.5 times higher for bacteremia, although there was no significant difference overweighing the annual fluctuations regarding Hib/Hi diseases (Table 1).[6,7]

The difference may be due to the climatic difference partly, but probably more to the differences of antibiotics use and blood culture practices, and its consequences. In outpatient clinics in Japan, antibiotics are commonly prescribed without blood cultures, especially in areas with few large medical facilities, such as Eastern Hokkaido. However, a blood culture is generally performed when the patient is admitted for acute febrile syndrome. We assume the frequent use of antibiotics differently affects the epidemiology, antibiotic resistance and possibly the progress of pneumococcal and Hib/Hi diseases.

The same assumption applies to differences in incidence between Japan and other developed countries. Compared with other developed countries, invasive pneumococcal diseases were more detectable than invasive Hib/Hi diseases in Hokkaido. This trend is more prominent when looking only at meningitis. The incidence of pneumococcal meningitis was 0.97–1.97 in Hokkaido, whereas that is 2.1–7.0 in Europe[8] and 3.6 in the United States.[8] The incidence of Hib meningitis was 6.02 in Hokkaido, whereas that is 12–22 in Europe[9] and 16–30 in the Americas.[9] Compared with other developed countries, the incidence of Hib meningitis is much lower in Hokkaido, but a substantial burden of this fatal disease was observed. Again, climate/geography may play a role in the relative differences in pneumococcal and Hib incidence, but it may also be due to frequent antibiotic use.

The reported incidence of pneumococcal bacteremia in children <5 years old in prefectures other than Hokkaido and Okinawa in 2008 to 2010 was 6.5–26.1[6,7] and that of invasive Hib/Hi diseases was 11.2–24.2.[6,7] In Hokkaido, the invasive pneumococcal disease incidence was 2- to 5-fold higher and invasive Hib diseases was higher than other prefectures, with the exception of some of the more heavily populated prefectures that might have admitted patients from neighboring prefectures. Differences in the data from the mainland and island prefectures most likely arise from the considerable flow of patients across prefectural borders. Many bacteremia cases also likely go unreported in some areas.

At the end of 2011, the estimated immunization coverage of the Hib vaccine in Hokkaido Prefecture by the manufacturers was 76% and that of PCV7 was 90%, but we saw no significant reduction in incidence of meningitis. However, from January 1 to October 31, 2012, only 1 case of bacterial meningitis (by group B Streptococcus) was reported to us. According to the Hokkaido Prefecture government, utilization of the prefecture's reimbursement system indicates that as of April 2012, over 95% of children <5 years old had been vaccinated with at least 1 dose of Hib vaccine and/or PCV7 (unpublished data). Although it is too early to state any evidence-based conclusions, we expect that the Hib vaccine and PCV7 will prove highly beneficial in Japan and believe it is important to strengthen surveillance to monitor their impact.

Note: The immunization coverage of PCV7 provided by the manufacturers is calculated as follows:

Vaccination coverage = number of vaccines sold in the area / number of children <5 year old.

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Note

Changes in nasopharyngeal carriage of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* among healthy children attending a day-care centre before and after official financial support for the 7-valent pneumococcal conjugate vaccine and *H. influenzae* type b vaccine in Japan

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ABSTRACT

The 7-valent pneumococcal conjugate vaccine (PCV7) and *Haemophilus influenzae* type b (Hib) vaccine reduce nasopharyngeal carriage of vaccine-type bacteria, which may in turn influence the presence of other nasopharyngeal bacterial pathogens. To investigate this possibility, nasopharyngeal carriage of potential pathogens was examined before and after official financial support was provided to offer the PCV7 and Hib vaccines in healthy children attending a day care centre in Japan during 2011–2012. Despite a virtual disappearance of PCV7 serotypes over time, the overall pneumococcal carriage rate remained unchanged. Although others have reported an increase in PCV13 serotypes following PCV7 vaccination, only non-PCV13 serotypes were observed to have increased in this study. The majority of *H. influenzae* isolates were non-typeable and Hib was not found. Our data identified an unexpected pattern of pneumococcal serotype replacement following PCV7. Continuous monitoring of pneumococcal carriage is important for decisions regarding the future of national vaccination policy in Japan.

The 7-valent pneumococcal conjugate vaccine (PCV7) and *Haemophilus influenzae* type b (Hib) vaccine prevent nasopharyngeal acquisition and transmission of 7 serotypes of pneumococci and Hib in children, respectively [1–3]. Vaccinating children with both PCV7 and Hib vaccines offers effective protection against invasive disease due to PCV7 serotypes and Hib in all age groups [3–5]. However, in many countries, the nasopharyngeal flora of PCV7-vaccinated children is immediately occupied by non-PCV7 but PCV13 serotype pneumococci either due to true replacement, unmasking, or capsular switch, resulting in a similar overall pneumococcal carriage rate [1]. As a result, PCV13 vaccination is now a prevailing strategy to prevent against severe pneumococcal disease, including invasive pneumococcal disease (IPD), in the US and Europe. In Korean children, *Streptococcus pneumoniae* serotype 19A is increasingly recognized as a cause of IPD prior to the introduction of PCV7 [6]. In Japanese children, rates of invasive pneumococcal disease (IPD) due to 19A and non-PCV13 serotypes increased soon after the introduction of PCV7 [7].

In Japan, the PCV7 and Hib vaccines were not approved by the Japanese Ministry of Health, Labor and Welfare until January of 2007 and 2008, respectively. Therefore, it was not possible to have children voluntarily vaccinated against Hib and PCV7 until late 2008 and 2009, respectively. In November 2010, the Japanese Ministry of Labour Health and Welfare established a Provisional Special Fund and recommended vaccination of children with Hib vaccine and PCV7 for the Urgent Promotion of Vaccination. After

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this, Hib vaccine and PCV7 were formally added to the immunization schedule for Japanese infants in 2013.

Since February 2011, Hib and PCV7 vaccines have been publically funded for children under 5 years old in Chiba Prefecture. However, because these vaccines were not yet widely accessible in Japan, vaccination rates among infants and younger children at risk were estimated to be 40–60% at the end of 2011. Therefore, the aim of this study was to investigate the nasopharyngeal carriage of bacteria in healthy children before and immediately after official financial support was provided for these vaccinations.

After obtaining written informed consent from at least one parent, a nasal swab was taken from the participating child and the parent was asked to complete a standardized short questionnaire. The study population consisted of 57 children.

Approval for this study was obtained from the Medical Ethical Committee of Chiba University (no.1120).

Children attending a day care centre at Chiba University Hospital were studied from February 2011 to October 2012 with nasopharyngeal swabs taken every 6 months. At least one of their parents worked at Chiba University Hospital. Parents of the participating children completed a brief survey about their PCV7 and Hib vaccination history. Samples of nasopharyngeal flora were obtained from the children with a nylon flocked flexible sterile Copan E-swab according to World Health Organization standard procedures [8]. After sampling, all swabs were directly inoculated in a liquid medium and plated within 1 h at the Microbiology Laboratory of Chiba University Hospital. All swabs were processed by the same laboratory and cultured to detect the presence of *S. pneumoniae, H. influenzae* and *Moraxella catarrhalis* according to standard bacteriological procedures for conventional cultures. One pneumococcal colony per plate was subcultured and serotyped by Quellung reaction using type-specific antisera from the Statens Serum Institute (Copenhagen, Denmark). To determine the sequence type (ST) of the isolates, multi-locus sequence typing (MLST) was performed as described previously [9]. STs were determined by an internet database search at http://spneumoniae.mlst.net/.

One *H. influenzae* colony per plate was subcultured and serotyped using a slide agglutination test using six monovalent antisera (serotypes a-f) manufactured by Remel (Remel Inc., Lenexa, KS, USA). Specimens were also inoculated on Hib antiserum agar prepared with Levinthal base and Hib antiserum as described previously [10].

SPSS statistics 18.0 software was used to examine differences in distribution between the studied populations. The crude odds ratio (OR) and Mantel–Haenszel OR stratified by age with 95% confidence intervals (CIs) were calculated using the χ^2 test. A P value of <0.05 was considered statistically significant.

Table 1 shows the baseline characteristics of the children who participated in the study. A total of 57 children aged from 5 months to 6 years were enrolled in the study. Twenty children participated once and 37 children participated more than once with 11, 22 and 4 children participating 2, 3 and 4 times, respectively. During the course of the study, no participants hospitalized with IPD or invasive Hib disease.

The number of non-immunized children and children vaccinated on a catch-up schedule gradually decreased, while the number of fully immunized children increased during this study.

S. pneumoniae, H. influenzae, M. catarrhalis and *Staphylococcus aureus* were isolated from nasopharyngeal culture as pathogenic bacterial species of interest. Because *S. aureus* was detected at a very low rate ($n = 6$), specific bacterial species refers to *S. pneumoniae, H. influenzae* and *M. catarrhalis* in this report. The distribution of carriage of each pathogen is shown in Table 2. Overall carriage rates of pathogenic bacteria were 47.6% ($n = 59$) for *S. pneumoniae*, 35.5% ($n = 44$) for *H. influenzae* and 58.1% ($n = 72$) for *M. catarrhalis*. No significant association was found between gender and colonization by specific bacterial species. The age-specific recovery of specific nasopharyngeal pathogens is shown in Fig. 1. *S. pneumoniae* and *M. catarrhalis* carriage rates were observed to decline with age, while *H. influenzae* carriage rates remained almost the same. Younger age (<24 months) was significantly associated with *S. pneumoniae* colonization (OR = 1.639, 95% CI 1.147–2.343, $P = 0.008$). Carriage of *H. influenzae* was not associated with age. *M. catarrhalis* declined with age and was significantly more prevalent among children

Table 1
Characteristics of the children participating in this study.

	Mar. 2011	Oct. 2011	Mar. 2012	Oct. 2012
Children	29	35	32	28
Male	18	20	22	16
Female	11	15	10	12
Age group				
<1 yr	2	4	3	0
1 yr	6	12	10	9
2 yr	9	8	8	9
3 yr	5	5	3	5
4 yr	2	2	4	4
>5 yr	5	4	4	1
PCV7 status				
Fully immunized (4 doses)	4	4	8	13
Catch up[a] (1–3 doses)	11	14	12	9
On going[b] (1–3 doses)	5	12	9	4
Not immunized[c]	9	5	3	2
Hib vaccine status				
Fully immunized (4 doses)	5	5	5	12
Catch up[a] (1–3 doses)	12	10	13	9
Ongoing[b] (1–3 doses)	8	16	12	7
Not immunized[c]	4	4	2	0

[a] Catch up: a child first vaccination started after 7 months old and finished with reduced doses.
[b] Ongoing: a child who has not completed his or her vaccination schedule.
[c] Not immunized: a child who has not been immunized.

Table 2
Characteristics of bacterial isolates.

	Mar. 2011	Oct. 2011	Mar. 2012	Oct. 2012	MLST (No. of isolates)
Total No. of *S. pneumoniae*	**16**	**15**	**14**	**14**	
PCV7 serotypes	7 (43.8%)	3 (20.0%)	1 (7.1%)	0 (0%)	
6B	4	2	0	0	ST902 (5)
					ST5233 (1)
19F	3	0	1	0	ST8454 (1)
					ST236 (3)
23F	0	1	0	0	ST242 (1)
Non-PCV13 serotypes	9 (56.2%)	12 (80.0%)	13 (92.9%)	14 (100%)	
23A	2	1	0	0	ST338 (3)
15A	1	2	1	2	ST63 (6)
15C	1	0	1	2	ST199 (4)
34	3	7	1	0	ST7388 (11)
35B	1	2	7	2	ST2755 (12)
37	1	0	0	0	ST447 (1)
15B	0	0	3	0	ST199 (3)
6C	0	0	0	3	ST2942 (1)
					ST5823 (2)
11A/E	0	0	0	3	ST8737 (3)
10A	0	0	0	1	ST5236 (1)
Non-typeable	0	0	0	1	ST4845 (1)
Total No. of *H. influenzae*	**5**	**4**	**24**	**11**	
Type d	0	0	0	1	
Type e	1	1	4	0	
Type f	1	0	0	0	
Nontypeable Hi	3	3	20	10	
Total No. of *M. catarrhalis*	**19**	**12**	**27**	**14**	

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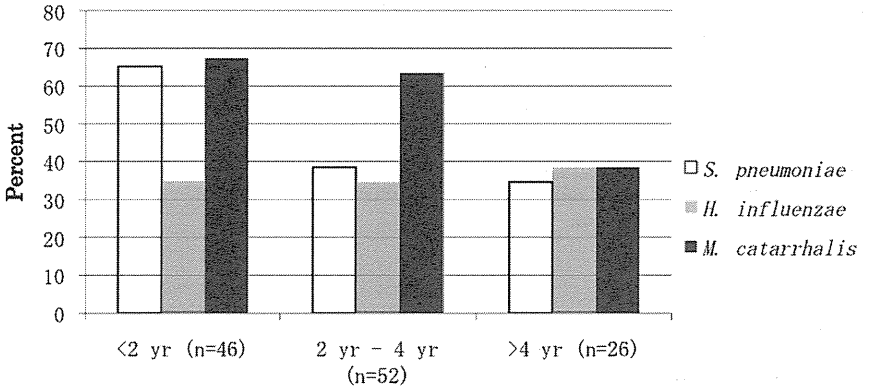

Fig. 1. Recovery of specific nasopharyngeal pathogens with age.

under 48 months (OR = 1.857, 95% CI 1.073–3.214 $P = 0.006$). Almost one third ($n = 45$, 36.3%) of the cases had only one respiratory pathogen. More than one pathogen was colonized in 56 cases (45.2%). Thirty-six cases (29.0%) had two respiratory pathogens and 20 children (16.1%) had three species. Even when the influence of age was eliminated using the Mantel–Haenszel test, a positive association was noted for co-colonization with *S. pneumoniae* and *M. catarrhalis* (OR 4.878, 95% CI 1.442–16.495, $P = 0.009$). No significant associations were observed between the presence of *H. influenzae* and colonization with the other two bacterial species.

We then analyzed the characteristics of 59 *S. pneumoniae* and 44 *H. influenzae* isolates. Near complete eradication of PCV7 serotype carriage was observed within 2 years of announcement of the Provisional Special Fund recommendation for PCV7 immunization. The 6B and 19F PCV7 serotypes were also effectively eliminated following vaccination (Table 2). Although previous studies have reported vaccination to produce an emergence of PCV13 serotypes 6A and 19A, only non-PCV13 serotypes were identified in this study. In PCV7 immunized children (including on going immunization schedule), 50 *S. pneumoniae* strains were isolated, whereas 9 *S. pneumoniae* strains were isolated from PCV7 non-immunized children. Forty-two non-PCV13-type strains and 8 PCV7-type strains were isolated from PCV7 immunized children. Six non-PCV13-type strains and 3 PCV7-type strains were isolated from unvaccinated participants. There was no significant association between the *S. pneumoniae* serotypes and PCV7 immunization status. There were 4 children who participated in this study 3 or 4 times, and carried a PCV7-type strain at the first culture. The PCV7 immunization status of all 4 children did not change during this study. Among them, one child acquired a non-PCV13-type strain and three did not carry any *S. pneumoniae* strains in the last culture. Furthermore, we performed MLST analysis and identified the sequence type (ST) of each serotype (Table 2). Most of isolates with the same serotype had one sequence type (ST).

Next, the capsular serotypes of 42 *H. influenzae* isolates were analyzed and 8 out of 42 (19%) of them were found to be capsulated, after which they were categorized as type d, e, or f (Table 2). No colony was identified on Hib antiserum agar.

Since bacterial colonization depends on numerous factors, including economic and environmental variables as well as host-related factors and vaccination effects, bacterial carriage rates vary widely among different studies and geographical sites [11]. The objective of the present study was to establish the prevalence and specific features of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* strains circulating amongst day care centre attendees in Japan.

In our study, a majority of children (81.5%) harbored at least one potential respiratory pathogen. Rates of Hib and PCV7 vaccination were high among subjects even before public funding became available. This might be attributable to greater interest among parents regarding their children's health, since at least one parent of each child was working at Chiba University Hospital.

This study shows that the risk of being colonized by *S. pneumoniae* is not associated with colonization by *H. influenzae* but positively associated with colonization by *M. catarrhalis*. The risk of being colonized by *H. influenzae* was not associated with colonization by *M. catarrhalis*, which is consistent with the findings of a previous report [12].

After the introduction of PCV7 vaccination, the prevalence of PCV13 serotypes 6A and 19A has been reported to increase, while PCV7 serotypes are known to become less dominant. PCV13, including serotypes 6A and 19A, replaced PCV7 in vaccination schedules in the US in 2010. Presently, PCV7 is being gradually replaced with PCV13 worldwide. In addition, an increase in non-PCV13 serotypes 15A and 22F has been reported in the US [13]. In our study, carriage of vaccine type strains decreased significantly after PCV7 vaccination became publically funded. Unlike the findings reported in the US and elsewhere, an increase in non-PCV13 serotypes, including serotypes 6C, 15A, 15C, 35B and 11A/E, was observed as opposed to PCV13 serotypes. A similar prevalence of pathogens has been reported in Japanese pediatric patients with IPD [7]. Spread of microorganisms is commonplace in the era of globalization. As such, replacement of the PCV7 vaccine with a PCV13 vaccine may have little efficacy, even in those areas that are currently observing emergence of PCV13 serotypes in the setting of PCV7 vaccination. Prevention and control of pneumococcal infections in young children will require the development of new vaccination strategies aimed at targeting additional serotypes or other antigens.

Introduction of Hib vaccination led to a significant reduction of Hib disease and carriage in both vaccinated and unvaccinated children due to a herd immune effect [14]. More than 80% of children in our study were vaccinated against Hib, and no Hib strain was recovered in any child. Kuroki et al. reported a Hib carriage rate of 0.84% among healthy Japanese children prior to introduction of the Hib vaccine [10]. Specific data regarding the prevalence of Hib carriage prior to introduction of the Hib vaccination are not available in this setting and the absence of Hib isolates is likely to be the result of a very low prevalence of Hib carriage alone. *H. influenzae* capsular type d, e and f were present in small amounts but detected every time. Invasive disease due to *H. influenzae* type d, e or f is rare, but needs to be considered as a possibility. Although a randomized controlled study reported that no changes in carriage rate with *H. influenzae* and *M. catarrhalis* were observed after vaccination with 2 or 3 of doses PCV7 [15], the carriage rate of *H. influenzae* and

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M. catarrhalis in this study seems to have increased after official financial support for the PCV7 and Hib vaccine was introduced. Higher PCV pressure following a 4 doses schedule and nationwide introduction in the routine infant vaccination schedule may induce bacterial shifts. We should monitor the colonization status of immunized children to evaluate this potential phenomenon.

Continuous surveillance of carriage of invasive disease pathogens will allow us to establish the effect of conjugate vaccine use on *S. pneumoniae* and *H. influenzae* serotype distribution.

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Conflict of interest

None.

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小児耳鼻咽喉科　2013; 34(3)　別刷り

細菌性髄膜炎予防ワクチン定期接種化のインパクトを考える

小児耳鼻咽喉科領域感染症への影響も含めて

石和田　稔　彦
（千葉大学医学部附属病院感染症管理治療部）

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シンポジウム4

予防接種のインパクト

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（千葉大学医学部附属病院感染症管理治療部）

小児に細菌性髄膜炎を惹起する2大原因菌は，インフルエンザ菌b型（Hib）と肺炎球菌である。また，Hibは急性喉頭蓋炎の主要な原因菌でもある。Hib，肺炎球菌による感染症を予防するワクチンは，世界中の国々で使用され劇的な効果をあげている。一方，日本においては2008年12月からHibワクチンが，2010年2月から7価肺炎球菌結合型ワクチン（PCV7）が使用可能となった。Hibワクチン，PCV7は，当初任意接種ワクチンとして導入されたが接種率が低く十分な予防効果が認められていなかった。しかし，2011年になり，全国的に公費助成が受けられる体制が出来たことから接種率が上昇し，髄膜炎をはじめとする重症感染症が全国的に減少している。今年両ワクチンが定期接種化されることで，更なる効果が期待される。今後ワクチンの有効性を正しく評価するためには，正確な罹患率調査と分離菌の莢膜型別解析が重要な課題である。

キーワード：髄膜炎，インフルエンザ菌b型ワクチン，7価肺炎球菌結合型ワクチン，莢膜型，小児

はじめに

細菌性髄膜炎は急激に進行する予後不良な疾患である。小児では典型的な臨床症状を呈さず，初期診断が困難なことが多い。また，適切な治療を行っても，永続的な後遺症を残すことや不幸にして亡くなることも多い。小児に細菌性髄膜炎を惹起する2大原因菌は，インフルエンザ菌と肺炎球菌であり，2007年～2008年の日本での小児細菌性髄膜炎に関する全国アンケート調査では，インフルエンザ菌が髄膜炎原因菌全体の57%，肺炎球菌が19%を占めていた[1]。これら2大原因菌に対する予防ワクチンである，インフルエンザ菌b型（Hib）ワクチンと，7価肺炎球菌結合型ワクチン（PCV7）が開発され，日本でも広く使用されるようになり，2013年4月から定期接種化された。本講演では，細菌性髄膜炎予防ワクチンの導入効果

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と今後の課題を中心に，小児耳鼻咽喉科領域感染症への影響も含め概説したい。

インフルエンザ菌感染症

インフルエンザ菌は6種類の莢膜型（a, b, c, d, e, f）と無莢膜株に分けられる。Hibは主に乳幼児に髄膜炎，喉頭蓋炎などの侵襲性感染症（血液や髄液から細菌が分離される感染症）を惹起する。Hib以外の莢膜型も侵襲性感染症を惹起するがその頻度は低い。一方，無莢膜株は小児及び成人の気管支炎，肺炎，中耳炎，副鼻腔炎，結膜炎などの局所感染症の主たる原因菌である。分離されたインフルエンザ菌がHibであるかどうかの判定は，熟練した細菌検査技師であればコロニーの性状から判別可能であるが，一般的には抗血清による凝集法もしくはPCR法を用いた判定が必要となる。しかし，莢膜型別は一般の医療機関では行われていない。私たちは，Hibワクチン導入前の小児インフルエンザ菌侵襲性感染症調査と分離株に対するPCR法を用いた莢膜型解析を行った[2]。その結果，小児インフルエンザ菌侵襲性感染症の中で髄膜炎は最も頻度が高く，その他の病型としては，菌血症，関節炎，喉頭蓋炎，肺炎が認められた。莢膜型の解析においては，Hibが侵襲性感染症の88.8%，髄膜炎の95.1%を占めており，日本においてもHibは髄膜炎を主体とするインフルエンザ菌侵襲性感染症の主体と考えられた。急性喉頭蓋炎は，耳鼻咽喉科との連携により診断，治療にあたる必要のある重要な小児救急疾患のひとつであるが，日本で原因菌に関するまとまった報告は少ない。2000年～2010年にかけて，東京都と千葉県の6施設で調査したところ，5歳以下の小児急性喉頭蓋炎の80%がHib菌血症を伴っていた[3]（図1）。この他，眼窩周囲蜂窩織炎もHibによるものが多いとされる。私たちは1985年から経年的に千葉県におけるインフルエンザ菌侵襲性感染症の罹患率調査を実施しているが，1985年5歳未満人口10万人あたり1.2であった罹患率は徐々に増加し，2005年には16.5となった[4]。

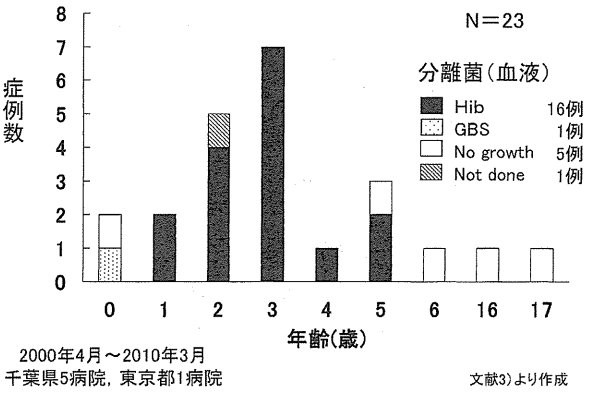

図1　急性喉頭蓋炎の原因菌と年齢分布

Hibワクチン

Hibワクチンは，Hibの病原性の主体となる莢膜多糖体（PRP）に破傷風菌のトキソイドを結合させ，乳児にも十分な免疫をつけることが出来るように工夫されたワクチンである。1987年に米国ではHibワクチンが導入され，患者数が減少したと報告されている[5]。また，フィンランドにおいては，Hibワクチン導入後，髄膜炎と共に急性喉頭蓋炎も激減したことが報告されている[6]。現在Hibワクチンは世界100か国以上で認可されている。このような状況の下，日本においてもHibワクチンの接種が2008年12月から可能となった。Hibワクチンの効能・効果はHibによる感染症予防であり，Hib以外の莢膜型と無莢膜株に対しての予防効果はない。日本におけるHibワクチンの接種対象者は，生後2カ月以上5歳未満で，推奨される接種開始時期は，生後2カ月～6カ月である。初回免疫を4～8週間隔（医師が必要と認めた場合には3週間隔でも可能）で3回行い，おおむね7～13カ月後に追加接種を1回行うことが標準的な接種スケジュールとなっている（図2）。Hibワクチン導入後の状況であるが，接種開始当初は，品不足や任意接種であったこともあり，接種率が伸びず明らかな予防効果は認められなかった。しかし，2011年から「子宮頸がん等ワクチン接種緊急促進臨時特例交付金制度」により，全国的に公費助成制度

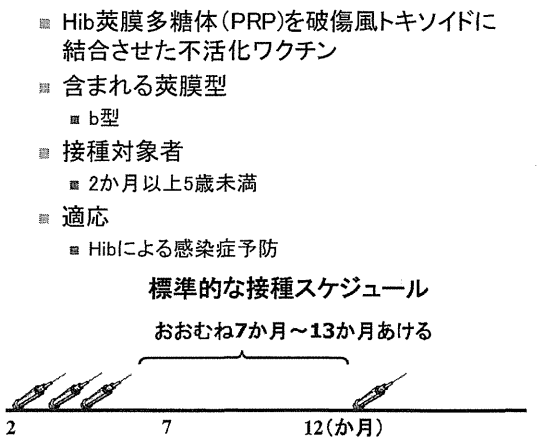

図2　インフルエンザ菌b型（Hib）ワクチン

が導入され大多数の市町村で5歳未満の小児に対して，Hibワクチンが無料で接種可能となった。ワクチンの出荷状況や公費助成制度導入後の市町村での推定接種率などから総合的に判断すると，Hibワクチンの接種率は公費助成制度導入後上昇していると考えられ，それに伴い髄膜炎をはじめとするインフルエンザ菌侵襲性感染症は，明らかに減少してきている。千葉県ではインフルエンザ菌による髄膜炎は，2010年30例発生していたが，2011年7例，2012年4例，2013年6月現在0例である。

肺炎球菌感染症

Hibワクチン，PCV7普及前の日本において小児細菌性髄膜炎の原因菌として，インフルエンザ菌に次いで多かったのが肺炎球菌である[1]。インフルエンザ菌と異なりほとんど全ての肺炎球菌は莢膜を有しており，莢膜型は現在93種類に分類される。莢膜型別は，インフルエンザ菌と同様一般の医療機関では実施されていない。肺炎球菌は，小児から成人に至るまで幅広い年齢層に侵襲性感染症も局所感染症も共に惹起するが，侵襲性感染症で最も頻度の高いものは菌血症ついで肺炎，髄膜炎の順となる。急性乳突洞炎も耳鼻咽喉科医との連携が必要となる重要な肺炎球菌関連疾患である。PCV7導入前の千葉県では2007年39例，2008年61例，2009年76例と年々肺炎球菌侵襲性感染症による入院例は増加傾向を認め，5歳未満人口10万人あたりの罹患率は2009年26.1に達した[7]。肺炎球菌菌血症は，外来症例を中心に検討するとより多いとする報告があり，西村らは菌血症の5歳未満人口10万人あたりの罹患率は328と推計している[8]。なお，肺炎球菌性髄膜炎に関しては，2007年～2010年における千葉県内の調査において，19例のうち，7例（29.0%）が後遺症を残し1例（3.1%）が死亡しており，予後不良例が多かった。

7価肺炎球菌結合型ワクチン（PCV7）

PCV7は4, 6B, 9V, 14, 18C, 19F, 23Fの7つの血清型の莢膜多糖体をジフテリア毒素の変異蛋白（ジフテリア CRM_{197}）に結合させたものであり，乳児にも十分な免疫が誘導できる。海外におけるPCV7導入前の小児侵襲性感染症症例から分離される肺炎球菌のPCV7カバー率は70%を超えており，実際米国では2000年にPCV7を導入した後，PCV7に含まれる莢膜型の肺炎球菌による侵襲性感染症は激減した[9]。日本におけるPCV7の効能・効果は，PCV7に含まれる血清型による肺炎球菌侵襲性感染症予防で，接種対象は生後2カ月～10歳未満であり，推奨される接種開始時期は生後2カ月～6カ月で，初回免疫を4～8週間隔で3回行い，生後12～15カ月に追加接種を行うというスケジュールになっている（図3）。PCV7導入後の状況に関して，PCV7導入前の国内の肺炎球菌に関する疫学調査結果からみるとPCV7に含まれる血清型別のカバー率は肺炎球菌全体の約70%となっており[10]，日本においてもPCV7を導入した場合，充分な効果が得られることが予想されていた。しかし，2010年2月からPCV7は使用可能となったもののHibワクチンと同様，任意接種の段階では接種率が伸びず，患者数は減少しなかった。公費助成が認められるようになってから，患者数は減り，千葉県では2010年肺炎球菌髄膜炎は10例発生していたが，2011年2例，2012例3例，2013年6月現在1例となっている。

- 7つの肺炎球菌莢膜多糖体をジフテリア毒素の変異蛋白（ジフテリアCRM$_{197}$）に結合させた不活化ワクチン
- 含まれる莢膜型
  - 4, 6B, 9V, 14, 18C, 19F, 23F
- 接種対象者
  - 2か月以上10歳未満
- 適応
  - PCV7に含まれる血清型による侵襲性肺炎球菌感染症予防

標準的な接種スケジュール

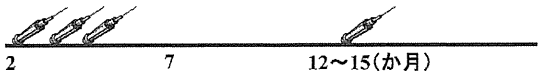

図3　7価肺炎球菌結合型ワクチン（PCV7）

PCV7の肺炎，中耳炎，保菌に対する影響

PCV7は導入後海外において，2歳未満の市中肺炎入院例が減少したこと[11]や肺炎球菌による中耳炎の罹患率を低下させたという報告がなされている[12]。日本では侵襲性感染症予防の適応しかないが，海外においては肺炎や中耳炎を予防適応疾患としている国も多く認められる。我々は，PCV7導入前の2008年と導入後の2012年，千葉市において小児市中肺炎の罹患率に関する調査を行ったところ，喀痰から肺炎球菌が有意に分離され，肺炎球菌性肺炎と考えられる入院例が減少し，分離された菌株をみると2012年は2008年に比べてPCV7に含まれる莢膜型が有意に減少していた。詳細な分析が必要ではあるが，PCV7が日本の小児市中肺炎の疫学に影響を与えていると考えている。中耳炎に関しては，PCV7導入前の小児急性化膿性中耳炎患者の中耳貯留液での分離菌の32％が肺炎球菌であり，分離された肺炎球菌のうち，62.7％がPCV7に含まれる莢膜型ということが報告されている[13]。今後PCV7導入の小児中耳炎に与える影響に関する検討の結果が待たれる。私たちは，PCV7が肺炎球菌保菌に与える影響について千葉大学医学部附属病院に併設されている保育園において保護者の同意のもと，園児の保菌調査を定期的に実施した（2011年2月，10月，2012年2月）。検討時期における園児のPCV7接種率は62.5％，86.9％，94.0％と上昇し，それに伴い，分離される肺炎球菌の中でPCV7に含まれる莢膜型の比率が，44.4％，20.0％，7.1％と減少した。ちなみにHibに関しては，初回調査時すでにHibワクチン接種率は84.4％に達しており，3回の保菌調査においてHibは1株も分離されなかった[14]。

表1　全国10道県の小児期侵襲性細菌感染症罹患率の推移

	2008～2010	2011	2012	減少率（％）2008～2010年と2012年の比較
Hib 髄膜炎	7.7	3.3	0.6	92
Hib 非髄膜炎	5.1	3.0	0.9	82
肺炎球菌髄膜炎	2.8	2.1	0.8	71
肺炎球菌非髄膜炎	22.2	18.1	10.6	52
GBS 髄膜炎	1.3	1.3	1.5	−15
GBS 非髄膜炎	1.2	1.1	1.2	0

罹患率：5歳未満人口10万人あたり
厚生労働科学研究費補助金　新しく開発されたHib，肺炎球菌，ロタウイルス，HPV等の各ワクチンの有効性，安全性並びにその投与方法に関する基礎的・臨床的研究　平成22～24年度　総合研究報告書P. 16から作成

今後の課題

千葉県を含む全国10道県において，厚生労働省の研究班（研究代表者：国立三重病院　庵原俊昭先生）によりHibワクチン，PCV7導入前から，インフルエンザ菌，肺炎球菌侵襲性感染症の疫学調査が行われている。この調査においても，千葉県と同様Hib，肺炎球菌の侵襲性感染症罹患率は，2011年になり減少傾向が認められており，公費助成によるワクチン接種率の上昇が大きく影響していると考えられる。一方，ワクチンのないB群レンサ球菌（GBS）侵襲性感染症の罹患率は変化が認められていない（表1）。今後の課題としてはワクチンの効果を正しく評価するための体制整備があげられる。幸い2013年4月1日より，感染症法施行規則改正に伴い，インフルエンザ菌侵襲性感染症および肺炎球菌侵襲性感染症は成人も含め5類全数届け出疾患となった。今後は全数調査の