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年 | 2011年 | 2012年 | 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　　（文献7）より作成）

## Ⅲ PCV7導入後の状況

千葉県では継時的に入院症例を主たる対象とした小児IPDのサーベイランスを実施しているが，PCV7導入後も任意接種の段階では患者数の減少はわずかであった．しかし，2011年2月から全県下で公費助成が認められ，5歳未満の小児に対してPCV7が無料で接種可能となった後，患者数，罹患率ともに低下傾向が認められている．とくに髄膜炎に関しては，2010年10例発生していたが，2011年2例，2012年3例と減少している．なお，千葉県を含む全国10道県においても，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PCV7導入前から，インフルエンザ菌侵襲性感染症，IPDの疫学調査が行われている．この調査においても，インフルエンザ菌b型（*Haemophilus influenzae* type b：Hib）侵襲性感染症，IPD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ている[6]．ちなみにワクチンのないB群レンサ球菌（GBS）侵襲性感染症に関しては，調査期間を通して罹患率の変化は認められていない（**表1**）[7]．

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[8]や肺炎球菌による中耳炎の罹患率が低下したことが報告されている[9]．日本ではIPD予防の適応しかないが，海外で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．われわれは，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PCV7に含まれる血清型の肺炎球菌の分離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．今後小児中耳炎に関してもPCV7導入の影響に関する検討の結果が待たれる．

## Ⅳ 予防接種法改正による変更点

予防接種法の改正によりPCV7は，2013年4月1日より定期接種となりA類疾病として実施されることになった．A類疾病は「ヒトからヒトに伝染することによるその発生及び蔓延を予防するため，またはかかった場合の病状の程度が重篤になり，もしくは重篤になるおそれがあるもの」として区分され，従来の1類疾病に相当する．A類疾病は国の積極的勧奨があり，保護者は子どもに受けさせるように努める義務（努力義務）があるワクチンである．また，万が一重篤な副反応が認められた場合，B類疾病にくらべ手厚い補償が受けられる．

表2　侵襲性肺炎球菌感染症検査方法届け出基準

| 検査方法 | 検査材料 |
|---|---|
| 分離・同定による肺炎球菌の検出 | 髄液，血液 |
| PCR 法による肺炎球菌の遺伝子の検出 | 髄液，血液 |
| ラテックス法またはイムノクロマト法による肺炎球菌抗原の検出 | 髄液 |

一方，IPD は感染症法施行規則改正に伴い，成人も含め5類全数届け出疾患となった．IPD の検査法による届け出基準を**表2**に示す．従来尿中抗原検出に用いられていたイムノクロマト法による肺炎球菌抗原検出キットの髄液での使用が保険収載されたことにより，イムノクロマト法による診断も届け出の基準に加えられている．

全数届け出になったことにより，成人も含め全国の IPD 罹患状況が明らかになることが期待される．発生届には，ワクチン接種歴を記載する項目が設けられており，肺炎球菌ワクチン接種の有無を確認することが必要となる．

## V 13 価肺炎球菌結合型ワクチン

PCV7 接種が普及した米国においては，PCV7 に含まれる血清型の IPD が減る一方，血清型 19A を中心に PCV7 でカバーされない血清型による IPD が増加し問題となっている[10]．この現象は，PCV7 を導入した他の国々でも認められており，韓国では，PCV7 導入前の 2004～2006 年の段階ですでに 19A による IPD の増加が報告されている[11]．国内における調査でも PCV7 導入後，全体の症例数は減少してきているものの，相対的に PCV7 でカバーされない血清型による IPD が増加してきており，海外と同様に 19A の割合が増えてきている[12]．

このような状況のもと，含有する血清型を 13 種類（PCV7 に含まれる血清型＋1，3，5，6A，7F，19A）まで増やした PCV13 が開発された．海外では PCV13 を認可し，PCV7 に代わり使用する国が主体となっており，PCV13 変更後の有効性が報告されている[13]．日本においても PCV13 は，2013 年 6 月に認可を受け今年度中に導入される予定となっている．**表3**に PCV7 と PCV13 の相違点を示す．両ワクチンの基本的な構造は同じであり，含まれる血清型が異なることとなる．PCV13 の接種対象年齢は 2 カ月～6 歳未満となっており，PCV7 にくらべ対象年齢が限定される（定期接種としての対象年齢は両ワクチンとも 2 カ月齢～5 歳未満）．ただし，PCV13 を 6 歳以上の小児に接種することに関しては，接種を妨げる科学的根拠は示されていない．なお，米国の予防接種の実施に関する諮問委員会（The Advisory Committee on Immunization Practices：ACIP）は，免疫不全，機能的または解剖学的無脾症，髄液漏，人工内耳を伴う 19 歳以上の者に関して，PCV13 接種を勧奨する方針としている[14]．

PCV7 から PCV13 への具体的な切り替え方法に関して**表4**に示す．PCV7 の 4 回接種完了者への PCV13 の補助的追加接種（supplemental dose）に関しては，米国の ACIP で推奨されている．日本においては費用対効果の観点から supplemental dose は定期接種としては認められなかったが，現在の IPD 原因菌の血清型分布を考えた場合，PCV7 接種完了者に対しても任意接種ワクチンとしての PCV13 接種を勧奨すべきであろう．

## おわりに

抗菌薬使用により細菌が薬剤耐性機構を獲得していったように，最近，肺炎球菌が莢膜遺伝子を組み換えることでワクチンの影響を回避しているという現象（capsular switching）が報告されている[15]．肺炎球菌感染症を予防するためのワクチンは肺炎球菌莢膜を用いて作られているため，IPD の血清型解析はワクチンの有効性をはかるうえ，また今後の予防戦略を考えるうえで重要である．しかしながら，血清型の解析

表3　7価と13価肺炎球菌結合型ワクチンの相違点

| | 7価肺炎球菌莢膜多糖体<br>蛋白結合型ワクチン | 13価肺炎球菌莢膜多糖体<br>蛋白結合型ワクチン |
|---|---|---|
| 略称 | PCV7 | PCV13 |
| 接種対象年齢 | 2カ月～10歳未満 | 2カ月～6歳未満 |
| 接種回数 | 計4回（0歳時3回＋1歳時1回）<br>ただし接種開始時期により接種回数が異なる | 計4回（0歳時3回＋1歳時1回）<br>ただし接種開始時期により接種回数が異なる |
| ワクチンの主成分 | 肺炎球菌の莢膜中に含まれる<br>多糖体にキャリア蛋白（ジフテリア $CRM_{197}$）<br>を結合したもの | 肺炎球菌の莢膜中に含まれる<br>多糖体にキャリア蛋白（ジフテリア $CRM_{197}$）<br>を結合したもの |
| 含まれる血清型 | 4，6B，9V，14，18C，19F，23F | 1，3，4，5，6A，6B，7F，9V，<br>14，18C，19A，19F，23F |
| 免疫誘導方法 | T細胞依存性の免疫反応<br>2歳未満の乳幼児に対して免疫誘導可能<br>ブースター効果あり | T細胞依存性の免疫反応<br>2歳未満の乳幼児に対しても免疫誘導可能<br>ブースター効果あり |
| 日本での認可 | 2009年認可 | 2013年認可 |

表4　7価から13価肺炎球菌結合型ワクチンへの移行スケジュール

| | 初回<br>1回目 | 初回<br>2回目 | 初回<br>3回目 | 追加接種 | 補助的<br>追加接種* |
|---|---|---|---|---|---|
| 標準接種月齢 | 2カ月 | 4カ月 | 6カ月 | 12～15カ月 | 6歳未満 |
| PCV7未接種者 | PCV13 | PCV13 | PCV13 | PCV13 | 不要 |
| PCV7 1回接種者 | PCV7 | PCV13 | PCV13 | PCV13 | 不要 |
| PCV7 2回接種者 | PCV7 | PCV7 | PCV13 | PCV13 | 不要 |
| PCV7初回接種完了者 | PCV7 | PCV7 | PCV7 | PCV13 | 不要 |
| PCV7接種完了者 | PCV7 | PCV7 | PCV7 | PCV7 | PCV13 |

*：任意接種ワクチンとして実施

にはコストと時間がかかるため，一般的には行われておらず一部の研究機関において実施されているのが現状である．今後はIPDから分離された菌株を保存し，血清型解析を積極的に行っていく体制を整えていく必要がある．

またPCV7はワクチン関連血清型の肺炎球菌の保菌を減らすことで，間接的な効果としてワクチンを受けていない人の肺炎球菌感染症を減らす効果も期待される．これは集団免疫効果といわれるもので，集団免疫効果は直接的な予防効果の2倍以上あるともいわれている．実際，PCV7導入後米国ではワクチン接種対象外の65歳以上の高齢者のIPDが減少したことが報告されている[16]．日本においても小児への肺炎球菌ワクチン接種率上昇に伴い高齢者のIPDが減少するのかを検証していく必要がある．

肺炎球菌は，小児から成人まですべての年齢層において重要な細菌である．長期的な感染予防の観点から，肺炎球菌ワクチンは小児科医と内科医が連携をもって対応方法を考えるべきワクチンとして位置づけられるべきであろう．

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原　著

# 細菌性髄膜炎患者のヒブワクチン，小児用肺炎球菌ワクチン普及前後の比較

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## 要　旨

北海道で小児期（0～15歳）に発症した細菌性髄膜炎の発症数を，ヒブワクチン，小児用肺炎球菌ワクチンの接種率の低かった2007～2011年の5年間（前期5年間）と，接種率が向上した2012年と比較した．

前期5年間の細菌性髄膜炎の発症は94例（男48例，女46例，年平均18.8例）で起因菌はインフルエンザ菌60例，肺炎球菌20例，B群溶連菌6例，大腸菌6例，その他2例（リステリア菌1例，髄膜炎菌1例）であった．2012年の細菌性髄膜炎の発症は2例（男1例，女1例）でその起因菌は肺炎球菌1例，B群溶連菌1例でありインフルエンザ菌はゼロであった．

全6年間に分離された肺炎球菌は18株が同定され2007年血清型23F，19F，6A，34がそれぞれ1株，2008年6B 1株，2009年6B 2株，19F 1株，2010年14型2株，19A 2株，2011年6B 1株，23F 2株，6C 2株，2012年6B 1株であった．市販されている7価肺炎球菌結合型ワクチン（PCV7）に含まれる血清型は12株（カバー率66.7%），今後市販予定の13価ワクチン（PCV13）は15株（カバー率83.3%）であった．

ヒブワクチン，小児用肺炎球菌ワクチンは2013年4月から定期接種ワクチンに採用されたが，今後ワクチン非接種者および被接種者における対象疾患罹患状況をきめ細かく検索する必要がある．

キーワード：細菌性髄膜炎，インフルエンザ菌b型，肺炎球菌，ヒブワクチン，
小児用肺炎球菌ワクチン

## はじめに

乳幼児を対象としたインフルエンザ菌b型（Hib）ワクチン（アクトヒブ®）が2008年12月，7価結合型肺炎球菌ワクチン（PCV7，プレベナー®）が2010年2月に市販された．これらのワクチン普及以前は諸外国，わが国とも小児の細菌性髄膜炎の起因菌は常に第1位をHibが第2位を肺炎球菌が占めていた[1]．しかしながらワクチンの普及以降欧米諸国ではこれらの起因菌による髄膜炎が激減した．一方わが国では両ワクチンの市販当初はいずれも任意接種対象ワクチンであったことから接種率が低迷していた．ところが2010年11月に「子宮頸がん等ワクチン接種緊急促進事業」のための補正予算が成立し，子宮頸がんワクチン，ヒブワクチン，小児用肺炎球菌ワクチン接種に伴う市町村の事業への国による助成が決まった．Hib，肺炎球菌髄膜炎の発症年齢のピークは乳児期にあることから，両ワクチンの初回接種を生後2か月にスタートし，且つ4週間をあけて計3dose接種する．さらに1歳を過ぎてから追加免疫（計4dose）する必要がある．この時期はDPT（2012年11月からはDPT-IPV）の接種時期とも大略一致することから，複数のワクチンを同時に接種するいわゆる同時接種が普及した．しかしながら2011年2，3月にヒブワクチン，小児用肺炎球菌ワクチンを同時接種された児の急死例が報告され，一時ワクチンの同時接種が回避された．このため両ワクチンの接種率向上には時間がかかり，北海道においては2011年の後半になってはじめて乳児期における両ワクチンの接種率が90%を超えた（2011年12月の生後7か月未満児の接種率はHibワクチン94.5%，小児用肺炎球菌ワクチン92.1%，札幌市保健福祉局しらべ）．

この研究は医療圏が独立している北海道を調査対象として，ワクチン普及前後の小児期細菌性髄膜炎の発症状況を調査してワクチンの予防効果を検証することを目的とした．

## 対象と方法

2006年10月小児科医が常駐しかつ入院施設を有する北海道内の病院64か所（2008年には59病院）の小児科医長あてに，研究目的を説明し協力をお願いした．

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内容は2007年1月1日以後に発症した小児期の細菌性髄膜炎患者の背景調査と起因菌調査である．脳脊髄液から細菌が分離された場合，細菌検査室を持つ施設では細菌を増菌し，外注する施設には外注業者によって増菌して，あらかじめ送付してあった返送用容器に起因菌を入れ症例票とともに返送してもらった．

細菌学的検索は一括北里大学で行った．インフルエンザ菌と肺炎球菌は，PBP(ペニシリン結合蛋白)の遺伝子変異をPCRキットであるインフルエンザ菌遺伝子検出試薬（湧永製薬株式会社）とペニシリン耐性肺炎球菌（PRSP）遺伝子検出試薬（湧永製薬株式会社）を用いて行った．その成績から生方ら[2)3)]の報告に基づいてインフルエンザ菌はgBLNAR（β-ラクタマーゼ非産生アンピシリン耐性菌），gLow-BLNAR（β-ラクタマーゼ非産生アンピシリン軽度耐性菌），gBLPAR（β-ラクタマーゼ産生アンピシリン耐性菌），gBLPCR-I(β-ラクタマーゼ産生アンピシリン/クラブラン酸耐性菌I型），gBLPACR-II（β-ラクタマーゼ産生アモキシリン/クラブラン酸耐性菌II型），gBLNAS（β-ラクタマーゼ非産生アンピシリン感受性菌），肺炎球菌はgPRSP（ペニシリン耐性肺炎球菌），gPISP（ペニシリン中間耐性肺炎球菌），gPSSP(ペニシリン感受性肺炎球菌）に分類した．インフルエンザ菌における莢型の判別はHib遺伝子の解析（Hasegawaら[4)]）とインフルエンザ菌免疫血清を用いた凝集試験によって行った．使用したキットはPASTEREX™Meningitis（BIO-RAD, France)である．肺炎球菌の血清型はPneumococcal antisera（Statens Serum Institute, Copenhagen, Denmark)，B群溶連菌の血清型はGBS型別用免疫血清（デンカ生研），髄膜炎菌の血清型はPASTEREX™Meningitis(BIO-RAD, France)を用いて行った．

本研究は国立病院機構三重病院の倫理委員会の承認を得て行った．

患者検体提供に関して病院内倫理委員会の審査を要するとの返答のあった施設には研究の趣旨を説明し，症例を記号化するなどの旨を説明して委員会の承認を得た．

## 結　果

1. 2007年1月1日～2011年12月31日（前期5年間）に発症した細菌性髄膜炎

2007年から5年間に北海道内34病院から94例（男48例，女46例年平均18.8例)の報告があった．起因菌別にみるとインフルエンザ菌によるものが60例(年平均12例)，肺炎球菌によるものが20例(年平均4例)，B群溶連菌（以後GBS）6例（年平均1.2例)，大腸菌6例(年平均1.2例)，その他2例(リステリア菌，髄膜炎菌各1例）であった．

脳脊髄液中から分離されたインフルエンザ菌株中54株の莢膜型が検査され53株（98.1%）がb型で，そのうちアンピシリン耐性遺伝子型は49株で検査され，gBLNAR 30株，gLow-BLNAR 7株，gBLPAR 2株，gBLPACR-I 3株，gBLPACR-II 6株，gBLNAS 1株であった．肺炎球菌は17株の血清型とペニシリン耐性遺伝子が検査され6A（gPISP）1株，6B（gPRSR）4株，14(gPISP)2株，19F(gPRSP)2株，19A(gPISP 1株，gPSSP 1株)2株，23F(gPRSP)3株，34(gPSSP)1株，6C（gPISP）2株であった．GBS 4株の血清型が検査されIb，III，IV，V各1株であった．髄膜炎菌の血清型はY/W135であった（表1)．

治療に使用された抗菌薬はABPC(アンピシリン)，PAPM/BP(パニペネム/ベタミプロン)またはMEPM(メロペネム)のいずれかとCTX(セフォタキシム)またはCTRX（セフトリアキソン）の併用が通常であった．予後を起因菌別にみるとインフルエンザ菌によるものに死亡1例，神経学的後遺症1例，高度難聴2例，肺炎球菌によるものに神経学的後遺症1例，難聴2例，水頭症1例，GBSによるもの神経学的後遺症2例（1例に尿崩症合併）であった．

2. 2012年1月1日～12月31日に発症した細菌性髄膜炎

2012年に北海道内2病院から2例（男1例，女1例)の報告があった．1例は肺炎球菌による9か月女児であり全経過18時間で死亡した．脳脊髄液から血清型6B(gPISP)が分離されたが小児用肺炎球菌ワクチンの接種歴はなかった．1例はGBSによる1か月男児であり後遺症なく軽快退院した．この年にはインフルエンザ菌による髄膜炎の報告はゼロであった(表2)(図1)．

3. 発症年齢分布

リステリア菌（2歳)，髄膜炎菌（6歳）による各1例を除いた94例の発症年齢を起因菌別に図示した．1歳未満の症例はさらに0～11か月別に示した（図2)．GBSによるものは生後0～2か月，大腸菌によるものは生後0～4か月に発症していた．インフルエンザ菌によるものは0歳児に最も多く25例(生後2か月1例からはじまり4か月と8か月に4例)，1歳15例，2歳8例，3歳4例，4歳6例，5歳2例であり，肺炎球菌によるものは0歳児に最も多く（生後1か月の発病1例を含む）10例，次いで1歳児5例，2歳3例，10歳2例，14歳1例であった．2011年までの5年間にインフルエンザ菌，肺炎球菌による5歳未満児の症例数はそれぞれ58例，18例であり10万人口あたり発症率はそれぞれ5.7, 1.7であった．

4. 肺炎球菌の血清型別分離状況

2007年から2012年までに脳脊髄液から分離された肺炎球菌のうち18株の血清型とペニシリン耐性遺伝

表1　細菌性髄膜炎の細菌学的検査所見

| | | |
|---|---|---|
| ◆インフルエンザ菌　b型　53/54（98.1%） | | |
| | gBLNAR | 30株 |
| | gLow-BLNAR | 7株 |
| | gBLPAR | 2株 |
| | gBLPACR-I | 3株 |
| | gBLPACR-II | 6株 |
| | gBLNAS | 1株 |
| ◆肺炎球菌　PCV7（12/18，66.7%）　PCV13（15/18，83.3%） | | |
| | 6A（gPISP，PCV13含有） | 1株 |
| | 6B（gPRSP4株，gPISP1株，PCV7含有） | 5株 |
| | 6C（gPISP） | 2株 |
| | 14（gPISP，PCV7含有） | 2株 |
| | 19A（gPISP1株，gPSSP1株，PCV13含有） | 2株 |
| | 19F（gPISP，PCV7含有） | 2株 |
| | 23F（gPRSP，PCV7含有） | 3株 |
| | 34（gPSSP） | 1株 |
| ◆GBS | | |
| | Ib，III，IV，V | |
| ◆髄膜炎菌 | | |
| | Y/W135 | |

表2　細菌性髄膜炎の起因菌別発症数と予後

| | 症例数 | インフルエンザ菌 | 肺炎球菌 | GBS | 大腸菌 | その他 |
|---|---|---|---|---|---|---|
| 2007年 | 21 | 11 | 6<br>水頭症　1<br>高度難聴　1 | 2 | 1 | 1<br>水頭症　1 |
| 2008年 | 18 | 13<br>高度難聴　1 | 1<br>神経後遺症　1 | 2<br>神経後遺症（尿崩症）　1 | 1 | 1 |
| 2009年 | 19 | 12<br>高度難聴　2 | 4 | 1<br>神経後遺症　1 | 2 | 0 |
| 2010年 | 18 | 13<br>死亡　1<br>神経後遺症　1 | 4 | 0 | 1 | 0 |
| 2011年 | 18 | 11 | 5<br>難聴　1 | 1 | 1 | 0 |
| 2012年 | 2 | 0 | 1<br>死亡　1 | 1 | 0 | 0 |
| | 96 | 60 | 21 | 7 | 6 | 2 |

北海道，2007～2012年

子を検査した．2007年には6A(gPISP)，19F(gPRSP)，23F（gPRSP），34（gPSSP）各1株，2008年には6B（gPRSP）1株，2009年には6B（gPRSP）2株，19F（gPRSP）1株，2010年には14（gPISP）2株，19A（gPISP1株，gPSSP1株)2株，2011年には6B(gPRSP)1株，6C（gPISP）2株，23F（gPRSP）2株，2012年には6B（gPISP）1株であった（表3）．

これらの肺炎球菌の血清型は市販されている7価結合型肺炎球菌ワクチン（PCV7）に含まれている血清型（4，6B，9V，14，18C，19F，23F)と比較するとカバー率は12/18(66.7%)であり，今後市販予定の13価結合型肺炎球菌ワクチン（PCV13）に含まれている血清型（PCV7プラス1，3，5，6A，7F，19A）と比較するとカバー率は15/18（83.3%）であった（図3)(図4)．

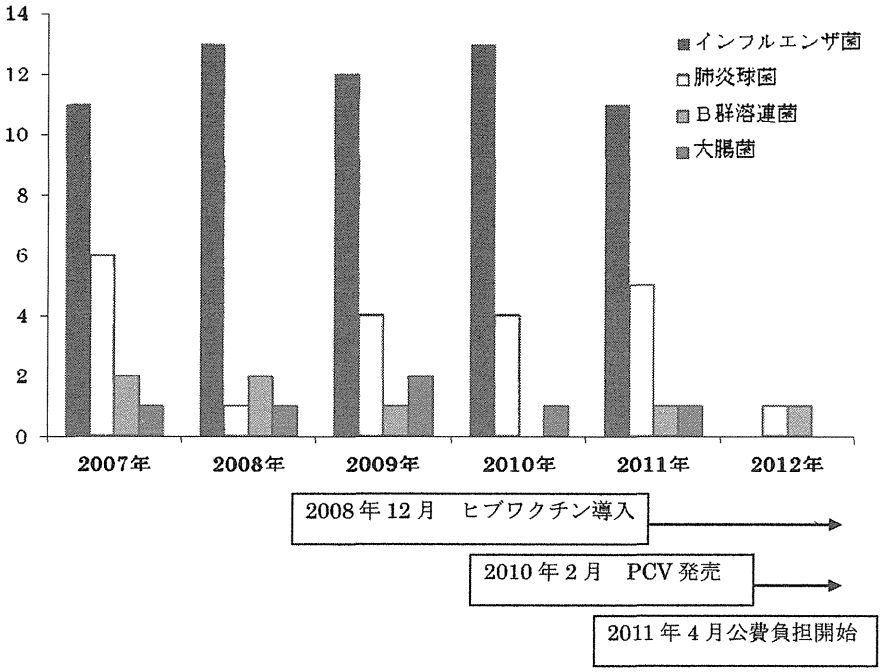


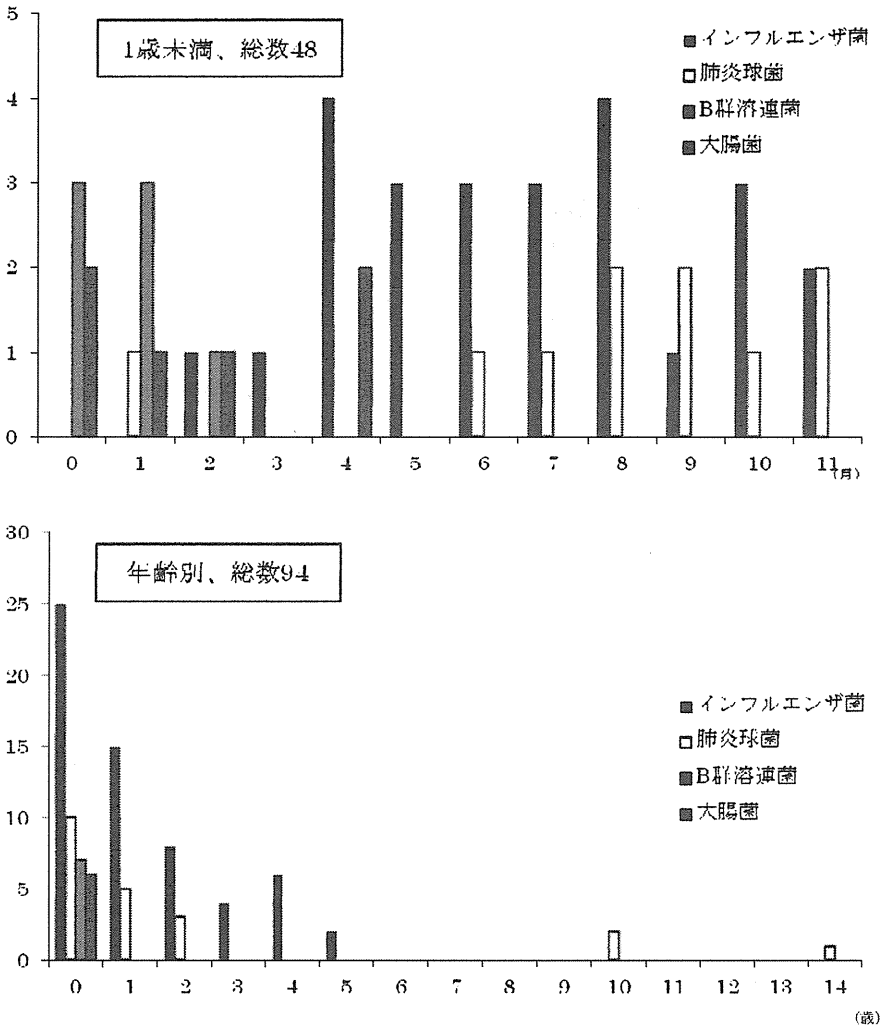

図1　細菌性髄膜炎の起因菌発症数の推移

## 考　察

筆者らは2006年秋に医療圏の独立している北海道における小児の細菌性髄膜炎の発症調査を企画した．これはヒブワクチン，小児用肺炎球菌ワクチンの普及によって，インフルエンザ菌，肺炎球菌を原因とする細菌性髄膜炎をはじめとする全身性感染症が激減した欧米諸国の事情を知っていたからである[5/6]．調査内容は2007年から小児期（0～15歳）に発症した全ての細菌性髄膜炎の起因菌収集と症例票収集である．

この結果2007～2012年の6年間に北海道内34病院小児科から96例（男49例，女47例）の症例が報告された．そして両ワクチンの接種率が90%を超えた2012年（生後7か月未満児の1dose以上接種）と，ワクチン接種率の低迷していた2011年までの5年間（前期5年間）との発症数を比較すると顕著な差を見出せることがわかった．すなわち前期5年間はインフルエンザ菌による髄膜炎が60例（年平均12例），肺炎球菌による髄膜炎が20例（年平均4例）発症したものが2012年にはそれぞれ0，1例に減少した（統計学的にはインフルエンザ菌で有意減少，肺炎球菌では有意ではない）．これらの症例の中でワクチン被接種者はそれぞれ1例ずつおり，2011年5月7日にヒブワクチン1dose目を接種した11か月女児が6日後の5月13日にHib髄膜炎を発症した症例と，2011年1月27日に小児用肺炎球菌ワクチン2dose目を接種した1歳女児が同年5月12日に肺炎球菌性髄膜炎を発症した症例である．前者は1dose接種6日後の発病であったことから，ワクチンによる抗体が産生される以前の発症と考えられた．また後者の脳脊髄液から分離同定された肺炎球菌の血清型がワクチン（PCV7）非含有型の6C（gPISP）と判明した．

インフルエンザ菌bと肺炎球菌は乳幼児の鼻咽頭に常在菌として存在し（健康キャリアー），ほんの一部の乳幼児が菌血症となり髄膜炎などの全身感染症をひきおこすと考えられる．両菌による細菌性髄膜炎の発生頻度は庵原[7]が10道県を調査して報告しており，5歳未満児10万人あたりHibが2010年7.8，2011年3.3，肺炎球菌が2010年2.3，2011年2.1とした．この発症頻度で推定すると全国でHib髄膜炎が2010年412例，2011年177例，肺炎球菌髄膜炎が2010年137例，2011年111例となった．この結果2011年ではヒブワクチン接種の効果が顕著であるが，肺炎球菌ワクチン接種の効果はまだ十分でないと結論している．筆者らのこのたびの報告では2011年にもインフルエンザ菌髄膜炎が11例，肺炎球菌髄膜炎が5例報告されており，これ以前4年間の発症頻度と変わりがない．両ワクチン接種に対する公費助成が行き渡り，乳幼児期の接種率が90%を超えた2012年にはHib髄膜炎，肺炎球菌髄膜炎がそれぞれ0，1例と激減した．環境からHib，病原性の強い肺炎球菌を無くするためには，幅広くワクチンを接種して集団免疫効果を得る必要があ




北海道、2007～2012年

図2　細菌性髄膜炎の起因菌別年齢分布

表3　肺炎球菌の血清型の推移

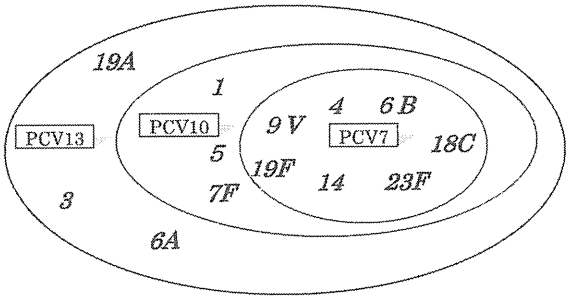
| | | 6B | 23F | 14 | 19F | 6A | 19A | 6C | 34 |
|---|---|---|---|---|---|---|---|---|---|
| 2007年 | 4 | | 1 | | 1 | 1 | | | 1 |
| 2008年 | 1 | 1 | | | | | | | |
| 2009年 | 3 | 2 | | | 1 | | | | |
| 2010年 | 4 | | | 2 | | | 2 | | |
| 2011年 | 5 | 1 | 2 | | | | | 2 | |
| 2012年 | 1 | 1 | | | | | | | |
| | 18 | 5 | 3 | 2 | 2 | 1 | 2 | 2 | 1 |

北海道，2007～2012年

る．

肺炎球菌は100に近い血清型の存在が知られている．このたび報告した北海道の髄膜炎症例から分離された肺炎球菌の血清型は，現在市販されている7価肺炎球菌ワクチン（PCV7）でカバーできる血清型が66.7%であった．2010年に血清型19A2株と2011年に

6C2株が分離された．この両株はPCV7が普及するにつれ欧米諸国で分離頻度が増加し，近年わが国でも増加している[8)9)]．19Aはわが国で間もなく認可発売予定の13価結合型肺炎球菌ワクチン（PCV13）に含有する血清型であり，6CはPCV13に含有する6Aと抗原性がクロスするという[10)]．欧米諸国では通常使用されている10価あるいは13価肺炎球菌ワクチンのわが国での早期採用が待たれる．また今後肺炎球菌による侵襲性全身感染症の発生動向を調査して，起因菌の血清型の推移を注意深く検索していく必要がある．




PCV7：(Wyeth,現 Pfizer)、93か国で発売(うち35か国で定期接種)
PCV10：(GSK) カナダ、ヨーロッパ、オーストラリアで承認済み
PCV13：(Wyeth,現 Pfizer) ヨーロッパ、アメリカで申請済み
※2009年3月31日現在

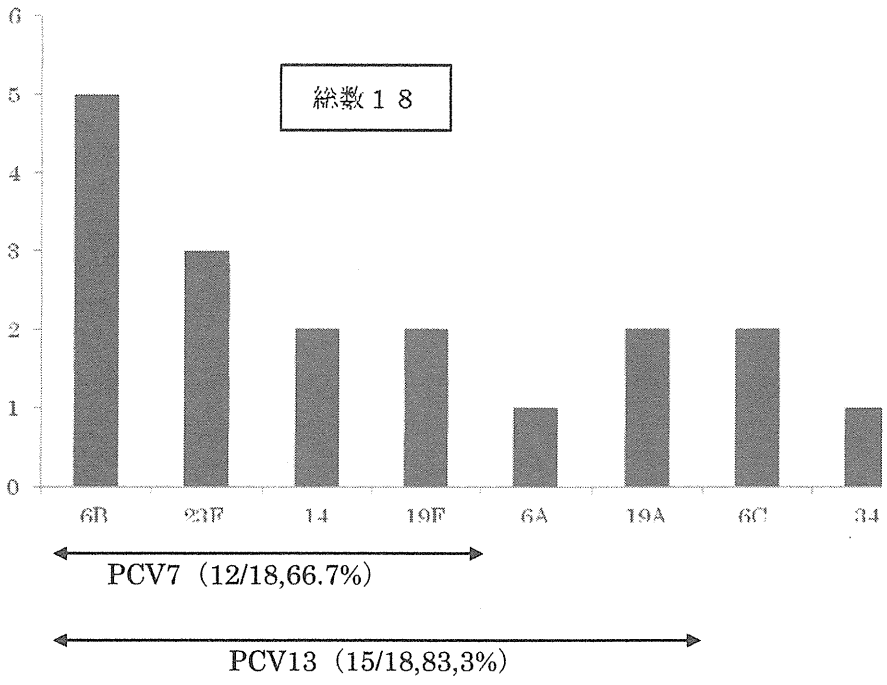
図3　肺炎球菌結合型ワクチンの血清型

## おわりに

2007～2012年の6年間に医療圏が独立している北海道で発症した小児の細菌性髄膜炎を報告した．2007～2011年の発症数は94例で，起因菌はインフルエンザ菌が60例(年平均12例)，肺炎球菌が20例(年平均4例)，GBSと大腸菌がそれぞれ6例（年平均1.2例），その他2例であった．ヒブワクチン，小児用肺炎球菌ワクチンの乳児期の接種率が90%を超えた2012年にはHib，肺炎球菌による髄膜炎はそれぞれ0，1例であった．両ワクチンは定期接種に採用されたが今後とも高い接種率を確保する必要がある．肺炎球菌ワクチンには多数の血清型が知られており，そのサーベイランスが今後の課題である．

症例報告と細菌収集は以下の小児科医(施設)からいただいた（敬称略，順不同）．

平野至規，新宅茂樹(名寄市立総合病院)，澤田博行，中山承代（北海道社会保険病院)，泉　岳，卯月ゆたか（帯広協会病院)，小林一郎(北見赤十字病院)，池本　亘(市立釧路総合病院)，長尾雅悦(国立西札幌病院)，岩井　崇，阿部修司(函館五稜郭病院)，濱野貴通，藤原伸一，佐藤泰征，森川俊太郎，小林義明（釧路赤十字病院)，飯田一樹（小樽協会病院）大島美保（札幌徳洲会病院)，藤原伸一，高梨久仁子，森岡圭太（帯広厚生病院)，古谷野　伸，杉本昌也(旭川医科大学病院)，窪田　満，北村勝誠（手稲渓仁会病




北海道、2007～2012年

図4　肺炎球菌血清型頻度

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，小簇菜穂，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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起因菌の収集管理は市立札幌病院検査部高橋俊司氏，症例表の管理・集計は伊藤　令氏によった．

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

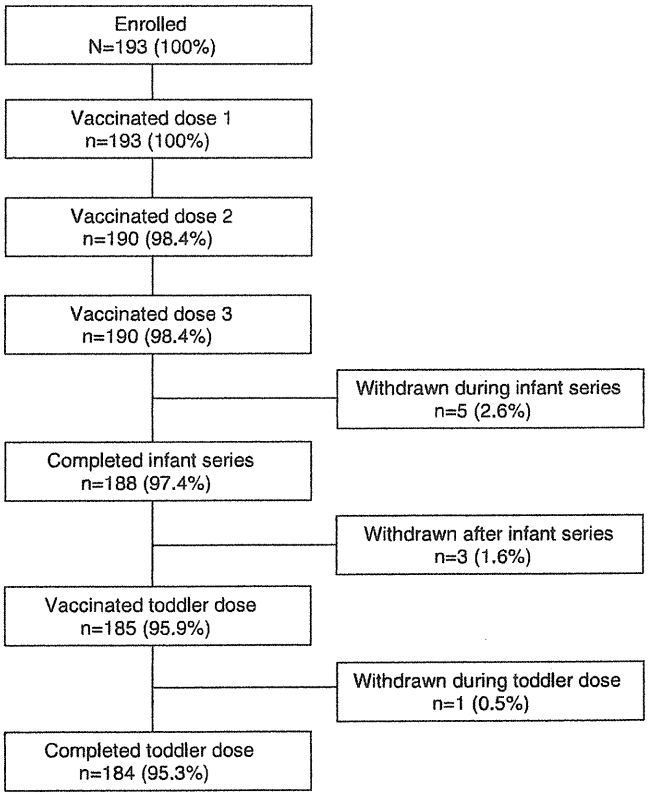


**FIGURE 1.** Subject disposition.

**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 | | | |
|---|---|---|---|---|
| | Dose 1 | Dose 2 | Dose 3 | Toddler Dose |
| 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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Our finding that hoarseness was associated with earlier diagnosis and higher band count in a subset of acute KD patients suggests that hoarseness may be a result of more severe systemic inflammation that also involves the larynx. Possible mechanisms for the hoarseness include transient inflammation of the larynx with associated edema of the true vocal folds, the development of vocal fold nodules and temporary recurrent laryngeal nerve paresis. Inflammation of the larynx as part of the overall systemic inflammation in acute KD is supported by several lines of evidence that suggest entry of the KD pathogen through the mucosa of the upper airway. First, computed tomography has documented diffuse enlargement of multiple lymph nodes most commonly in the anterior cervical chain often associated with retropharyngeal edema during the acute phase KD.[7–9] Second, case reports have documented uvulitis, supraglottitis and pulmonary nodules associated with acute KD.[1,10,11] Finally, an oligoclonal IgA immune response suggests entrance of the pathogen through the mucosal surfaces of the oropharynx and upper airway and virus-like inclusion bodies in respiratory epithelial cells may be related to the causative agent.[12,13] It is also plausible that KD may cause a transient recurrent laryngeal nerve paresis resulting in weakness of one of the vocal folds and associated hoarseness in some patients. Transient paresis of cranial nerves in KD is uncommon but well-reported and may involve cranial nerves VI, VII and VIII.[14,15] These palsies are transient and resolve in the subacute phase of the illness. Our limited observations of 3 patients by laryngoscopy did not suggest recurrent laryngeal nerve paresis as the etiology of the hoarseness in those patients. The laryngoscopic findings suggest that the hoarseness could be due to pathologic changes in the true vocal folds.

We recognize several strengths and weaknesses of our study. A strength of the study is that data were collected prospectively by 1 of only 2 clinicians (J.C.B. and A.H.T.) using a standardized data collection form that was completed at the time of admission. Outpatient evaluation was performed at standard intervals for all patients, and clinical assessments were performed by the same physicians. Study limitations include the lack of formal voice assessment by a pediatric speech pathologist. The commonly used adult rating scale, GRBAS (Grade, Roughness, Breathiness, Aesthenia, Strain), could not be applied due to the young age of our patients. Finally, the small number of laryngoscopies precludes our ability to make general statements about the mechanism of hoarseness in these patients. Another limitation is that comprehensive viral studies were not performed on the majority of patients so we cannot exclude concomitant viral upper respiratory tract infection as the cause of hoarseness in some of the KD patients.

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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 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