Incidence of Pneumococcal Bacteremia Requiring Hospitalization in Rural Thailand

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Background. Population-based estimates of the incidence of invasive pneumococcal disease are unavailable for Thailand and other countries in Southeast Asia. We estimated the incidence of pneumococcal bacteremia cases requiring hospitalization in rural Thailand.

Methods. Blood cultures were performed on samples from hospitalized patients in 2 rural provinces where active, population-based surveillance of community-acquired pneumonia is conducted. Blood cultures were performed at clinician discretion and were encouraged for all patients with suspected pneumonia and all children aged <5 years with suspected sepsis. Pneumococcal antigen testing was performed on positive blood culture specimens that failed to grow organisms on subculture.

Results. From May 2005 through June 2007, 23,853 blood culture specimens were collected overall, and 7319 were collected from children aged <5 years, which represented 66% and 47% of target patients, respectively. A total of 72 culture-confirmed pneumococcal bacteremia cases requiring hospitalization were identified. An additional 44 patients had media from positive blood cultures that yielded no growth on subculture but that had positive results of pneumococcal antigen testing. Of the 116 confirmed cases of bacteremia, 27 (23%) occurred in children aged <5 years; of these, 9 (33%) were confirmed by antigen testing only. The incidence of pneumococcal bacteremia cases requiring hospitalization among children aged <5 years had a range of 10.6–28.9 cases per 100,000 persons (incidence range if cases detected by antigen are excluded, 7.5–14.0 cases per 100,000 persons).

Conclusions. Invasive pneumococcal disease is more common than was previously suspected in Thailand, even on the basis of estimates limited to hospitalized cases of bacteremia. These estimates, which are close to estimates of the incidence of hospitalized cases of pneumococcal bacteremia in the United States before introduction of pneumococcal conjugate vaccine, provide important data to guide public health care policy and to inform discussions about vaccine introduction in Thailand and the rest of Southeast Asia.

Pneumococcal disease causes an estimated 1.6 million deaths globally each year, with up to 1 million deaths among children aged <5 years [1]. Of all vaccine-preventable deaths among children aged <5 years, 28% are attributable to pneumococcal disease [2]. The World Health Organization estimates that 716,000 deaths from pneumococcal disease among children aged <5 years could be prevented with full implementation of pneumococcal conjugate vaccines [2]. In a 2007 position statement, the World Health Organization recommended inclusion of 7-valent pneumococcal conjugate vaccine (PCV7) in national immunization programs [1].

Despite the safety and efficacy of PCV7, its use in low- and middle-income countries is limited [1]. PCV7 is currently not included in Thailand's Expanded Program on Immunization but is available in the private sector. The high relative cost of PCV7 in Thailand (3800 baht [~122 US$] per dose) and competing priorities for childhood vaccination programs have restricted its

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use. Moreover, limited local and regional data on pneumococcal disease burden and the lack of cost-effectiveness studies hamper informed decision making about the value of vaccine usage in many areas of the world, including Thailand and the rest of Southeast Asia.

Accurate surveillance data are needed to estimate the burden of invasive pneumococcal disease (IPD) and to inform decision making about vaccine policy in Thailand and the rest of Southeast Asia. Several cross-sectional and retrospective studies have documented the antimicrobial susceptibilities and serotype distributions of invasive and colonizing pneumococcal isolates in the region [3–5], but there are no published estimates of the incidence of pneumococcal disease. A recent study in Thailand demonstrated a high prevalence (60%) of nasopharyngeal carriage of *Streptococcus pneumoniae* among children aged <5 years [5], which suggests that the bacterium is common and that the prevalence of colonization is similar to that in countries before the introduction of pneumococcal conjugate vaccine and in other countries without routine vaccination. Passive, laboratory-based surveillance of invasive pneumococcal isolates is ongoing, to monitor trends in antimicrobial resistance and serotype distribution [3], but many hospitals in Thailand lack systems to reliably culture *S. pneumoniae,* making these data of limited value for estimating incidence. Although calculation of the overall disease incidence would require counting patients with pneumonia and bacteremia who were not hospitalized, hospital surveillance data are helpful in determining minimum estimates of IPD burden in Thailand and can be used to inform discussions about vaccine introduction.

The International Emerging Infections Program (IEIP), a collaboration between the Thailand Ministry of Public Health and the US Centers for Disease Control and Prevention, conducts active, population-based surveillance of hospitalized pneumonia cases in 2 rural Thailand provinces [6]. In 2005, building on this surveillance infrastructure, IEIP established state-of-the-art automated blood culture systems to support estimation of the incidence of IPD among hospitalized patients.

METHODS

Setting. IEIP conducts surveillance of community-acquired pneumonia cases requiring hospitalization in 2 rural provinces. Sa Kaeo Province (population, 526,432 persons; 33,150 aged <5 years) is adjacent to Cambodia in eastern Thailand, and Nakhon Phanom Province (population, 734,000 persons; 50,109 age <5 years) borders Laos in northeastern Thailand [7]. Surveillance is conducted at all 18 district and military hospitals (with 10–140 inpatient beds) and at both provincial hospitals (225 and 327 inpatient beds). Automated blood culture systems were established in Sa Kaeo (in May 2005) and in Nakhon Phanom (in November 2005) to improve diagnosis and management of disease among hospitalized patients by providing access to reliable performance of blood cultures at all hospitals. Since September 2006, health care services for eligible Thai citizens have been free of charge at public facilities; before that time, all essential services were available for a fee of 30 baht (~0.97 US$).

Patients. Clinicians requested blood culture specimens from hospitalized patients as was clinically indicated. In addition, IEIP encouraged blood cultures for all hospitalized patients with suspected pneumonia and for patients aged <5 years with possible sepsis, by reimbursing hospitals for costs of culture for these patients. Blood culture specimens were not collected from outpatients. Detailed clinical and demographic information was available for patients who were included in the IEIP pneumonia surveillance system as having clinical pneumonia (evidence of acute infection plus signs or symptoms of respiratory illness) [6]. Limited data (age, province, and initial diagnosis) were available for patients who had blood cultures performed but who were not captured by the pneumonia surveillance system.

We estimated the total number of hospitalized patients with clinical indications for blood culture as the sum of (1) all hospitalized patients with clinical pneumonia [6], (2) patients aged <5 years with possible sepsis (determined by review of inpatient hospital logs), and (3) any other patients who had a blood culture performed.

Patients who had blood cultures performed were classified using Pneumococcal Vaccines Accelerated Development and Introduction Plan (PneumoADIP) clinical case definitions for pneumonia [8], adapted to fit the available data. Pneumonia cases were subcategorized by severity and confirmation by chest radiograph (CXR), and categories were mutually exclusive. All patients with "pneumonia" had cough or dyspnea. Patients with "very severe pneumonia" additionally had ⩾1 danger sign (convulsions, intubation, or supplemental oxygen) or were aged <2 months with tachypnea or chest indrawing. Patients with "severe pneumonia" did not have danger signs but did have chest indrawing. Patients with "very severe pneumonia" and "severe pneumonia" were further classified as having "CXR confirmed" or "probable" pneumonia, depending on whether CXR findings were consistent with pneumonia or were negative or CXR was not performed. Patients with no danger signs and no chest indrawing but positive findings of CXR were classified as having "CXR-confirmed pneumonia." Patients with no danger signs, no chest indrawing, and with CXR either not done or with negative findings were classified as having "probable pneumonia" only if they had tachypnea. Patients with cough or dyspnea who did not meet any of these definitions were classified as "no pneumonia," as were all patients with no cough or dyspnea. Patients with no available detailed clinical information were classified as cases with "clinical data not available." Tachypnea was defined for children aged <5 years in accordance

with PneumoADIP guidelines [8] and by a respiration rate >30 breaths/min in patients aged ⩾5 years [9]. We did not collect CSF specimens and therefore did not report meningitis clinical syndrome. IEIP surveillance case definitions differed from those of PneumoADIP and were not used to classify patients for this report.

At the time of specimen collection, information on antibiotic use in the previous 72 h was recorded. Determination of antibiotic use was based on patient self-report and a nurse's review of medications received at the hospital before blood collection.

Specimen collection and laboratory methods. Blood cultures were performed using the BacT/ALERT 3D automated culture system (bioMérieux). All culture specimens were processed at the provincial hospitals. Culture specimens collected at the district and military hospitals were maintained at 15°C–30°C and were transported within 24 h to the provincial hospitals for processing. Each patient aged ⩾5 years provided ~20 mL of aseptically collected blood that was divided equally into a bottle for aerobic growth (FA bottle; bioMérieux) and a bottle for enhanced growth of mycobacteria, fungal pathogens, and other fastidious agents (MB bottle; bioMérieux). Each patient aged <5 years submitted ⩽10 mL of aseptically collected blood that was inoculated first into a pediatric bottle for aerobic growth (PF bottle; bioMérieux) and, if sufficient blood remained, into an MB bottle. Inoculated bottles were incubated according the manufacturer's protocol with use of Observa, version 1.1 (bioMérieux), to monitor and identify bottles meeting the criteria for positive growth (i.e., were alarm positive). Media from alarm-positive bottles were subcultured by standard methods to presumptively identify pathogens, including pneumococcus [10]. Bottles that signaled a positive alarm between midnight and 8 A.M. were not subcultured until laboratory staff returned at 8 A.M.. Liquid media from alarm-positive blood cultures with no growth on subculture were tested for *S. pneumoniae* antigen with use of an immunochromatographic test of pneumococcal antigen (NOW *S. pneumoniae* Antigen Test; Binax). This off-label use of the Binax NOW assay was performed using the manufacturer's instructions for testing urine and has been described elsewhere [11].

Confirmatory identification of *S. pneumoniae* was performed at the reference laboratory of the Thailand Ministry of Public Health. Serotype analysis was performed using a recently validated multiplex PCR assay series and was confirmed by the quellung reaction at the Centers for Disease Control and Prevention [12–16]; quellung results were used in cases with discrepancies. Antimicrobial susceptibilities were determined by the disk-diffusion method with the MIC values of selected antibiotics determined by E test (AB Biodisk) [10, 17]. Susceptibility interpretations were confirmed using the Clinical and Laboratory Standards Institute (CLSI) 2008 guidelines for nonmeningitis isolates of pneumococcus (penicillin susceptible, MIC ⩽2 μg/mL; intermediate, MIC of 4 μg/mL; resistant MIC ⩾8 μg/mL) [18, 19].

Pneumococcal bacteremia. Cases of pneumococcal bacteremia were defined by isolation of *S. pneumoniae* from blood or by positive results of pneumococcal antigen testing of alarm-positive blood culture media that failed to yield any organism on subculture. In a separate related study involving the same population, patients aged ⩾18 years with pneumonia submitted urine samples for pneumococcal antigen testing with Binax NOW. Patients with positive results of urinary antigen tests were considered to have pneumococcal pneumonia but were not included in estimates of bacteremia incidence. These findings are reported here to demonstrate the frequency of pneumococcal pneumonia cases not detected by blood culture.

Statistical analysis. We calculated the observed (i.e., minimum) incidence of pneumococcal bacteremia cases requiring hospitalization in each province, using midyear 2006 population estimates from the National Economic and Social Development Board of Thailand [7]. Incidence estimates were calculated for November 2005–June 2007. For months that occurred twice during this time period, cases were averaged, and a single monthly case count was used to calculate annual incidence. Exact 95% CIs were calculated on the basis of a Poisson distribution. Statistical analyses were done using SPSS, version 12.0 (SPSS). Proportions were compared using the χ^2 test.

RESULTS

From May 2005 through June 2007, 20,206 hospitalized patients in Sa Kaeo had indications for blood culture; 9582 (47%) of the patients overall and 2060 (23%) of the 8784 patients aged <5 years had blood cultures performed (table 1). In Nakhon Phanom, in November 2005–June 2007, 14,271 (89%) of all 16,080 hospitalized patients with indications for blood culture and 5259 (79%) of the 6689 patients aged <5 years had cultures performed. The total number of patients with blood culture performed in both provinces was 23,853. In Sa Kaeo, 3717 (39%) of the patients who had blood cultures performed were included in the IEIP pneumonia surveillance system and had clinical details available, whereas 9414 (66%) of patients who had blood cultures performed in Nakhon Phanom were included in the surveillance system (table 1). Patients in Sa Kaeo were more likely than were those in Nakhon Phanom to have elevated WBC counts (48% vs. 34%; $P < .001$) and to have evidence of severe or complicated illness (defined by requirement of supplemental oxygen, receipt of mechanical ventilation, thoracentesis, pneumonectomy, or death) (44% vs. 27%; $P < .001$). Among the 23,853 total patients who had blood culture performed, 7620 (32%) received antibiotics during the 72 h before obtainment of the culture specimen, according to patient or nurse report. The rate of antibiotic use among pa-

Table 1. Characteristics of patients who had blood specimens collected for culture in the Sa Kaeo and Nakhon Phanom provinces, Thailand, May 2005–June 2007.

Patient group, characteristic	Sa Kaeo Province	Nakhon Phanom Province
All patients (n = 23,853)	9582	14,271
Age		
<5 years	2060 (21.5)	5259 (36.9)
0–11 months	1200 (12.5)	1983 (13.9)
12–23 months	385 (4.0)	1432 (10.0)
24–59 months	475 (5.0)	1844 (12.9)
⩾5 years	7522 (78.5)	9012 (63.1)
5–14 years	566 (5.9)	1606 (11.3)
15–29 years	700 (7.3)	937 (6.6)
30–59 years	2936 (30.6)	3085 (21.6)
60–69 years	1313 (13.7)	1432 (10.0)
⩾70 years	2007 (20.9)	1952 (13.7)
Patients included in IEIP pneumonia surveillance[a] (n = 13,131)	3717	9414
Age <5 years	786 (21.1)	3692 (39.2)
Male	2028 (54.6)	5000 (53.1)
Documented fever (temperature >38.2°C)	1375 (37.0)	3370 (35.8)
History of fever	3400 (91.5)	8663 (92.0)
Documented hypothermia (temperature <35.5°C)	1 (0.0)	15 (0.2)
Elevated WBC count[b]	1689/3517 (48.0)	2680/7768 (34.5)
WBC count <3000 cells/mm^3	102 (2.9)	160 (2.1)
Cough	2451 (65.9)	7315 (77.7)
Hemoptysis	88 (2.4)	133 (1.4)
Dyspnea	1442 (38.8)	4207 (44.7)
Tachypnea[c]	588 (15.8)	1478 (15.7)
Rales or crepitation on lung examination	864 (23.2)	2451 (26.0)
Evidence of acute infection[d]	3527 (94.9)	8817 (93.7)
Signs or symptoms of respiratory illness[e]	2909 (78.3)	7979 (84.8)
Evidence of acute infection and respiratory illness[d,e]	2754 (74.1)	7450 (79.1)
Evidence of complicated illness	1628 (43.8)	2507 (26.6)
Supplemental oxygen needed	1555 (41.8)	2469 (26.2)
Receipt of mechanical ventilation	638 (17.2)	354 (3.8)
Thoracentesis	126 (3.4)	53 (0.6)
Pneumonectomy	17 (0.5)	1 (0.0)
Death	436 (11.7)	184 (2.0)

NOTE. Data are no. (%) of patients. IEIP, International Emerging Infections Program.

[a] Detailed clinical information was available for these patients.

[b] Elevated WBC count was defined as follows: for age <5 years, WBC count >15,000 cells/mm^3; for age 6–17 years, WBC count >13,500 cells/mm^3; and for age >17 years, WBC count >11,000 cells/mm^3.

[c] Tachypnea was defined as follows: for age 0–2 months, respiration rate >60 breaths/min; for age 3–11 months, respiration rate >50 breaths/min; for age 1–4 years, respiration rate >40 breaths/min; and for age ⩾5 years, respiration rate, >30 breaths/min.

[d] Evidence of acute infection was defined as any of the following: documented fever, history of fever, documented hypothermia, elevated WBC count, or WBC count <3000 cells/mm^3.

[e] Signs or symptoms of respiratory illness were defined as any of the following: cough, sputum production, hemoptysis, chest pain, dyspnea, tachypnea, abnormal breath sounds, rhonchi, wheezing, or rales or crepitation on lung examination.

tients aged <5 years (33%) was similar to that among patients aged ⩾5 years (32%).

Laboratory findings. The median time from blood culture collection to placement in the BacT/ALERT 3D system (i.e., time to incubation) was 5.9 h and was longer for culture specimens collected in district hospitals (8.3 h) than for those collected in provincial hospitals (3.2 h). Among alarm-positive cultures, the median time to subculture was 0.52 h for bottles

that signaled a positive alarm between 8 A.M. and midnight but was longer (2.9 h) for bottles that signaled a positive alarm between midnight and 8 A.M..

Pneumococcal bacteremia cases requiring hospitalization. A total of 72 culture-confirmed pneumococcal bacteremia cases were identified in the 2 provinces (31 in Sa Kaeo and 41 in Nakhon Phanom) (table 2). Of 374 alarm-positive blood culture media with no growth on subculture, 337 (90%) were tested for pneumococcal antigen; 44 (13%) were positive by antigen testing (4 [19%] of 21 in Sa Kaeo and 40 [38%] of 106 in Nakhon Phanom). Of the total 116 bacteremia cases, 27 (23%) occurred among children aged <5 years, including 9 (33%) cases detected by antigen testing only. Pneumococcal bacteremia cases confirmed only by antigen detection had culture specimens with a longer median time from blood collection to incubation (7.9 vs. 3.9 h; $P < .01$, by Mann-Whitney U test) and a longer median time from a positive alarm to subculture (1.8 vs. 0.56 h; $P = .02$), compared with cases with cultures that yielded *S. pneumoniae*. The median time from blood collection to incubation was longer in Nakhon Phanom than in Sa Kaeo (6.7 h vs. 4.4 h; $P < .01$). During this time period, urinary antigen testing for pneumococcus was performed for 3118 patients with pneumonia who were aged ⩾18 years, and 149 (4.8%) had positive results; 112 (75%) of these 149 patients

Table 2. Blood culture results by clinical syndrome in the Sa Kaeo and Nakhon Phanom provinces, Thailand, May 2005–June 2007.

	Sa Kaeo Province			Nakhon Phanom Province		
Age group, characteristic	Total	*Streptococcus pneumoniae* isolated by culture	Positive by antigen testing[a]	Total	*S. pneumoniae* isolated by culture	Positive by antigen testing[a]
Age <5 years	2060	5 (0.2)	1 (0.0)	5259	13 (0.2)	8 (0.2)
Pneumonia						
CXR confirmed, very severe	141	0 (0.0)	0 (0.0)	372	2 (0.5)	1 (0.3)
Probable, very severe	168	0 (0.0)	0 (0.0)	544	2 (0.4)	2 (0.4)
CXR confirmed, severe	10	0 (0.0)	0 (0.0)	53	0 (0.0)	0 (0.0)
Probable, severe	11	0 (0.0)	0 (0.0)	62	0 (0.0)	0 (0.0)
CXR confirmed	68	0 (0.0)	0 (0.0)	672	2 (0.3)	0 (0.0)
Probable pneumonia	52	0 (0.0)	0 (0.0)	215	0 (0.0)	1 (0.5)
No pneumonia	336	1 (0.3)	0 (0.0)	1774	5 (0.3)	2 (0.1)
ND[b]	1274	4 (0.3)	1 (0.1)	1567	2 (0.1)	2 (0.1)
Age ⩾5 years	7522	26 (0.3)	3 (0.0)	9012	28 (0.3)	32 (0.4)
Pneumonia						
CXR confirmed, very severe	331	5 (1.5)	0 (0.0)	615	8 (1.3)	4 (0.7)
Probable, very severe	720	4 (0.6)	0 (0.0)	926	2 (0.2)	6 (0.6)
CXR confirmed, severe	2	0 (0.0)	0 (0.0)	12	0 (0.0)	0 (0.0)
Probable, severe	6	0 (0.0)	0 (0.0)	30	0 (0.0)	0 (0.0)
CXR confirmed	164	3 (1.8)	0 (0.0)	597	3 (0.5)	3 (0.5)
Probable pneumonia	83	0 (0.0)	0 (0.0)	166	0 (0.0)	1 (0.6)
No pneumonia	1625	3 (0.2)	1 (0.1)	3376	4 (0.1)	8 (0.2)
ND[b]	4591	11 (0.2)	2 (0.0)	3290	11 (0.3)	10 (0.3)
All ages	9582	31 (0.3)	4 (0.0)	14,271	41 (0.3)	40 (0.3)
Pneumonia						
CXR confirmed, very severe	472	5 (1.1)	0 (0.0)	987	10 (1.0)	5 (0.5)
Probable, very severe	888	4 (0.5)	0 (0.0)	1470	4 (0.3)	8 (0.5)
CXR confirmed, severe	12	0 (0.0)	0 (0.0)	65	0 (0.0)	0 (0.0)
Probable, severe	17	0 (0.0)	0 (0.0)	92	0 (0.0)	0 (0.0)
CXR confirmed	232	3 (1.3)	0 (0.0)	1269	5 (0.4)	3 (0.2)
Probable pneumonia	135	0 (0.0)	0 (0.0)	381	0 (0.0)	2 (0.5)
No pneumonia	1961	4 (0.2)	1 (0.1)	5150	9 (0.2)	10 (0.2)
ND[b]	5865	15 (0.3)	3 (0.1)	4857	13 (0.3)	12 (0.2)

NOTE. Data are no. (%) of patients. CXR, chest radiograph; ND, no clinical data available.

[a] Media from positive blood cultures that failed to yield an organism on subculture were tested using an immunochromatographic test of pneumococcal antigen (NOW *S. pneumoniae* Antigen Test; Binax).

[b] Patients not captured in the International Emerging Infections Program pneumonia surveillance system did not have adequate clinical information available to categorize.

also had blood cultures performed, but only 7 (6%) had confirmation by isolation of *S. pneumoniae,* and none had alarm-positive, subculture-negative blood cultures with positive results of antigen testing.

The annual incidence of hospitalized pneumococcal bacteremia overall was 3.7 and 7.6 cases per 100,000 persons in Sa Kaeo and Nakhon Phanom, respectively (figure 1). The incidence was highest among persons aged <5 years (10.6 and 28.9 cases per 100,000 persons, respectively).

Serotype distribution and antibiotic susceptibility. Among 72 patients with *S. pneumonia* isolated by blood culture, 2 patients had >1 colony with different serotypes (1 patient had 3 serotypes isolated and 1 patient had 2 serotypes isolated). One isolate was not available for typing, so a total of 74 pneumococcal isolates were typed. The most common serotypes were 14 (18%), 6B (14%), 3 (11%), and 19A (9%). Approximately 51% of serotypes were serotypes included in PCV7, 58% in 10-valent pneumococcal conjugate vaccine (PCV10) [20], and 81% in the 13-valent conjugate vaccine (PCV13) currently in clinical trials [21] (figure 2). Among the 19 isolates from children aged <5 years, the most common serotypes were 14 (26%), 6B (21%), 19F (16%), and 23F (6%); of these, 79%, 84%, and 95% were serotypes included in PCV7, PCV10, and PCV13, respectively.

With use of CLSI 2008 criteria for invasive isolates causing nonmeningitis infections, all isolates were susceptible to penicillin (with use of pre-2008 criteria [penicillin susceptible, MIC $\leq$0.06 μg/mL], 30 [41%] of 74 were nonsusceptible). Reduced susceptibility (intermediate or resistant interpretations) was documented to cotrimoxazole (55%), erythromycin (30%), and clindamycin (20%). Vaccine serotypes had a higher prevalence of reduced antibiotic susceptibility than did nonvaccine types (figure 3).

DISCUSSION

We report the first population-based estimates of the incidence of pneumococcal bacteremia in Southeast Asia. Because our surveillance includes only hospitalized patients (and does not include patients with other sterile-site infections), these findings

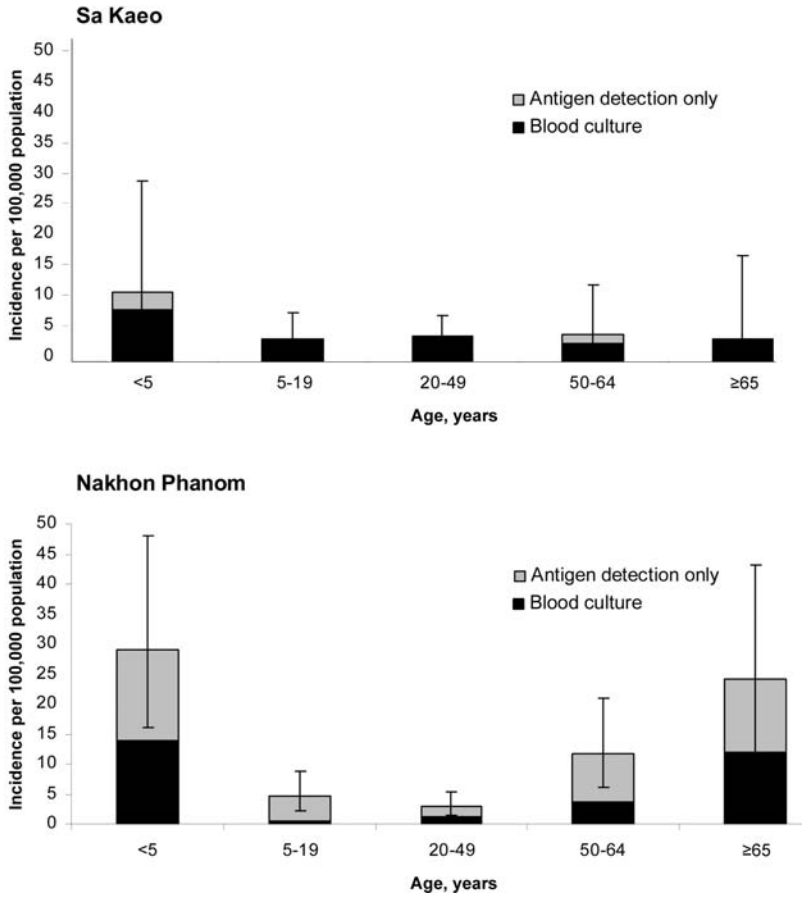

Figure 1. Annualized incidence of pneumococcal bacteremia cases requiring hospitalization in the Sa Kaeo and Nakhon Phanom provinces, Thailand, November 2005–June 2007. "Antigen detection only" refers to patients who had positive blood culture media that failed to grow a pathogen on subculture but that tested positive by an immunochromatographic test of pneumococcal antigen (NOW *Streptococcus pneumoniae* Antigen Test; Binax) [11].

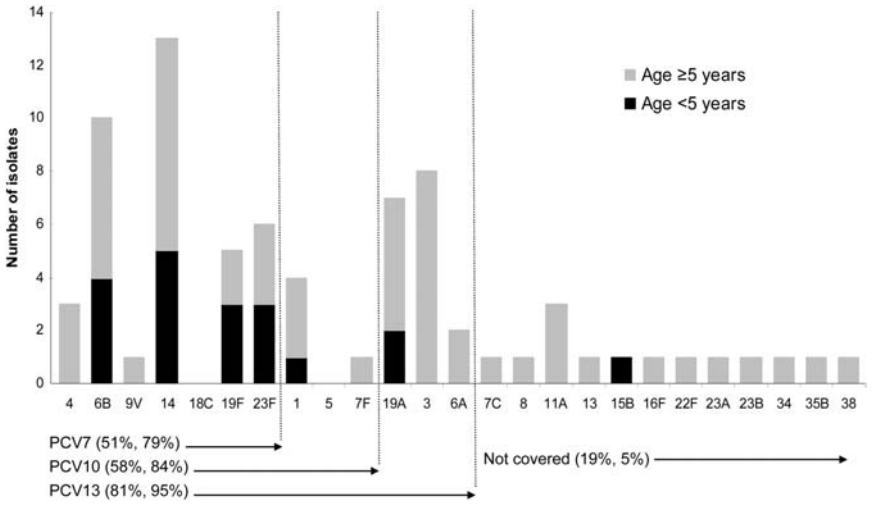

Figure 2. Serotype distribution of pneumococcal bacteremia isolates, according to serotypes contained in the 7-, 10-, and 13-valent pneumococcal conjugate vaccines (PCV7, PCV10, and PCV13, respectively). The values in parentheses are the percentage of vaccine serotypes among all invasive isolates and the percentage among isolates in specimens from children aged <5 years. A total of 74 isolates were obtained from 71 patients. Two patients had >1 serotype identified from a single bloodstream infection (one patient had 3 serotypes identified; the other had 2). The isolate from 1 patient was not available for typing.

substantially underestimate the true incidence of pneumococcal bacteremia (and IPD), especially among young children, who typically experience high rates of outpatient pneumococcal bacteremia [22]. Despite this limitation, our findings suggest that pneumococcal bacteremia is as common in Thailand as in some other countries where the decision was made to introduce PCV7 [23, 24]. These data can be used to guide public health care policy and to inform discussions about pneumococcal conjugate vaccine introduction in Thailand and Southeast Asia.

To our knowledge, there have been no other published studies estimating the incidence of pneumococcal bacteremia or the overall incidence of IPD in Thailand or any other Southeast Asian country. A prospective study of febrile patients in 1 hospital in Laos identified only 6 patients with pneumococcal bacteremia (3 were children aged 1–15 years) during a 5-year period [25]. Similarly, small numbers of cases were identified in our study areas before our project started—3 cases identified in 4 years in Sa Kaeo and 13 cases identified in 2 years in Nakhon Phanom—which highlights the fastidious nature of *S. pneumoniae* and the importance of effective laboratory systems to maximize isolation and of routine requests for blood culture by health care providers.

Even with modern equipment and rigorous quality assurance, our case detection was likely hampered by limitations unique to these settings. For instance, delayed specimen incubation during long transit times and delayed subculture of bottles that signaled a positive alarm overnight when technicians were unavailable could foster autolysis of pneumococcal isolates. Half of the blood culture specimens from district hospitals were collected >8.3 h before incubation, and although we sought to keep cultures at 15°C–30°C before incubation and during transport, exposure to higher temperatures could have occurred. These types of limitations may explain why some studies in Asia have had lower-than-expected *S. pneumoniae* yields [25] and why 38% of our cases were detected only by antigen testing of blood culture media that signaled a positive alarm but had negative results of subculture. Previous studies have found that 1%–10% of blood cultures processed in au-

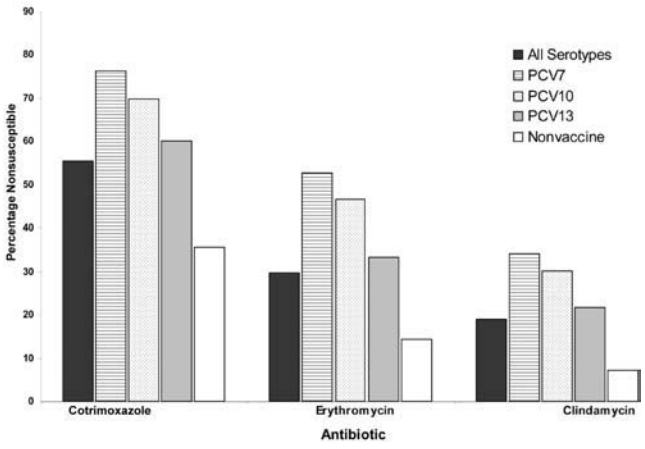

Figure 3. Antibiotic susceptibility of pneumococcal bacteremia isolates, according to serotypes contained in the 7-, 10-, and 13-valent pneumococcal conjugate vaccines (PCV7, PCV10, and PCV13, respectively). With use of the Clinical and Laboratory Standards Institute 2008 guidelines for nonmeningitis isolates of pneumococcus, all isolates were susceptible to penicillin. With use of pre-2008 guidelines, 30 (41%) of the 74 isolates were nonsusceptible to penicillin.

tomated culture systems generate positive signals but yield no growth on subculture [26, 27], which has been ascribed to factors such as antibiotic use before culture and elevated patient leukocyte counts. Pathogenic bacteria, including *S. pneumoniae,* have been confirmed by molecular assays in these subculture-negative blood cultures [27], supporting the plausibility of the pneumococcal bacteremia cases detected only by antigen testing of liquid media. Although this is not a licensed use of the Binax NOW test, at least 1 study found that it had excellent sensitivity and yielded few false-positive results [11]. Additional work is needed to assess the usefulness of rapid antigen-based assays for detection of *S. pneumoniae* in blood and serum samples.

Additional limitations of our surveillance system likely led to a further underestimation of the true incidence of hospitalized cases of pneumococcal bacteremia. Blood culture specimens were collected on the basis of clinician judgment, and culturing practices varied. Only 66% of patients with clinical indications for blood culture had culture performed (47% of patients aged <5 years). The higher percentage of patients who had culture performed in Nakhon Phanom (89%), compared with Sa Kaeo (47%) (for patients aged <5 years, 79% vs. 24%, respectively), likely accounted for higher numbers of cases detected in Nakhon Phanom. We also documented extensive use of antibiotics before obtainment of blood specimens, and we previously found that *S. pneumoniae* was isolated in culture >5 times more often from patients without prior antibiotic treatment than from patients with prior antibiotic treatment [28].

Given these limitations, our findings indicate that the incidence of hospitalized cases of pneumococcal bacteremia in Thailand among children aged <5 years is consistent with that in other countries that have introduced PCV7. In the United States, the incidence of hospitalized cases of pneumococcal bacteremia among children aged <5 years before PCV7 introduction was 31.4 cases per 100,000 persons (Active Bacterial Core Surveillance, Centers for Disease Control and Prevention, unpublished data), which is slightly higher than our estimate for Thailand of 10.6–28.9 cases per 100,000 persons. The prevaccine incidence in the United States among children aged <5 years more than triples, to 96 cases per 100,000 persons, when all cases of IPD (including outpatient bacteremia and inpatient meningitis cases) are included [29, 30]. The true IPD incidence in Thailand is likely similar. In Australia, before widespread use of PCV7, the incidence among children aged <5 years was 47.3 cases per 100,000 persons [24]. Although moderately higher than our estimates for Thailand, the incidence in Australia was based on all reported IPD cases, whereas in Thailand, we captured only hospitalized cases of pneumococcal bacteremia. The estimated prevalence of HIV infection among adults aged 15–49 years in Thailand is 1.4% [31], which we do not believe had a substantial impact on the epidemiology of pneumococcal bacteremia as described here. Furthermore, Thailand has a very successful program to prevent mother-to-child transmission of HIV, minimizing the impact of HIV on pneumococcal disease epidemiology in young children.

Although based on only 19 cases, 79% of pneumococcal bacteremia isolates from children aged <5 years were caused by serotypes included in PCV7, which is similar to what was demonstrated in the United States before PCV7 introduction [22]. Our findings suggest that vaccine coverage would be greater with PCV10 (84% coverage) or PCV13 (95% coverage), now in phase III clinical trials [21]. Although all pneumococcal isolates were susceptible to penicillin, reduced susceptibility to cotrimoxazole and erythromycin occurred in 55% and 30% of isolates, respectively. These percentages are consistent with recent analysis of carriage [5] and invasive isolates [3, 5] in Thailand. As in previous studies, we found that the proportion of resistant isolates was highest for those with vaccine serotypes. Because PCV7 introduction has been shown to reduce the prevalence of antimicrobial resistance among pneumococcal isolates causing invasive disease, this would be an additional benefit of vaccine introduction [32, 33].

The World Health Organization recommends that PCV7 be considered a priority for all national immunization programs [1]. Data on the local burden of pneumococcal disease are important for making decisions about vaccination schedules (e.g., catch-up schedules) and for evaluation of the impact of vaccine after introduction. Although our data underestimate the extent of IPD cases preventable by vaccine, the incidence estimates are consistent with those for hospitalized cases of pneumococcal bacteremia in the United States before PCV7 introduction, suggesting that the overall burden may be similar. Furthermore, children in Thailand experience high rates of radiographically confirmed pneumonia (~2000 cases per 100,000 children aged <5 years [6]), and probe studies demonstrate that the greatest impact of vaccine is on pneumonia [34]. Previous studies suggest that <5% of children aged <5 years with pneumococcal pneumonia have bacteremia [34], so pneumonia cases detected by blood culture represent a small fraction of the cases that could be prevented by vaccine. Finally, because PCV7 prevents disease in unvaccinated groups [27], the impact of vaccine may be even greater in Thailand, where the incidence of pneumonia among adults is also high [6].

Because the cost of PCV7 is high, compared with that of childhood vaccines currently in Thailand's Expanded Program on Immunization, creative financing mechanisms are needed to support vaccine introduction in middle-income countries such as Thailand, where its impact could be substantial. Vaccine cost-effectiveness studies are also needed in this setting, including consideration of indirect vaccine effects, which substantially increase the cost-effectiveness of childhood vaccination [35, 36]. Additionally, because our data are from rural sites, IPD surveillance in urban settings could help to inform further the decision-

making process regarding vaccines. Ongoing population-based surveillance remains important, to monitor IPD incidence, serotype distribution, and antimicrobial resistance, both before and after introduction of pneumococcal conjugate vaccine.

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