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The incidence of pneumonia in rural Thailand[☆]

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Summary

Background: Pneumonia continues to be a leading infectious disease killer, yet accurately measuring incidence remains a challenge. In 2002, Thailand began active, population-based surveillance for radiographically confirmed pneumonia in Sa Kaeo Province.
Methods: Full-time surveillance officers conducted active case ascertainment at every hospital, and routine audits and a community cluster survey promoted complete and accurate reporting. A case of pneumonia was defined as acute infection with signs or symptoms of lower respiratory tract infection and evidence of new infiltrates. An independent panel of radiologists reviewed digital images of all radiographs.
Results: Between September 2002 and August 2003, 777 patients met the case definition. The measured minimum incidence was 177/100 000 but the estimated incidence was as high as 580/100 000 with full adjustment for incomplete chest radiography and access to health care. Seventy-two (9%) patients died and 28% were known to be HIV positive. Fifteen (2%) patients had pneumonia twice during the year. The average cost of hospitalization for an episode of pneumonia ranged from US$490.80 to $628.60.
Conclusions: Pneumonia is a significant and costly public health problem in Thailand. This surveillance system allows precise assessment and monitoring of radiologically confirmed pneumonia and lays the groundwork for the introduction of new vaccines against pneumonia pathogens.
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Introduction

The World Health Organization (WHO) ranks acute respiratory illness, including pneumonia and influenza, as the top infectious disease killer worldwide, causing 3.5 million deaths, over half of which are in children under 5 years old.[1,2] Accurate data on pneumonia incidence are challenging to

obtain; a recent comprehensive review of the literature found that only 46 of the over 2000 published studies on pneumonia include estimates of incidence.[3] Population-based studies of pneumonia that allow accurate ascertainment of disease incidence and mortality are needed for estimating pneumonia burden, identifying changes in pneumonia patterns, and evaluating pneumonia interventions. Population-based surveillance coupled with comprehensive laboratory diagnostics are also needed to identify the burden of pathogen-specific causes of pneumonia. In many parts of the world, the great human and financial costs associated with such a surveillance system preclude its consideration.

Over the past two decades, there has been little progress in the treatment and control of pneumonia. Despite the availability of new vaccines in some wealthy countries, pneumonia remains the leading infectious killer among children in much of the world, and the approaches to treatment and prevention have changed little since the 1980s. Beginning in 1981, the World Health Organization promoted a simple clinical management approach for children that consisted of counting respiratory rate and checking for chest indrawing before administering antimicrobial therapy.[4] A number of important changes have occurred since then, including the development of vaccines to prevent some infectious causes of pneumonia, including *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and influenza virus, discovery of new pathogens, such as hantavirus, metapneumovirus, and SARS coronavirus, and new treatment approaches, such as short-course ampicillin. These changes in the understanding, treatment, and prevention of pneumonia have not resulted in a new global agenda for controlling pneumonia, perhaps in part because the burden in the most affected parts of the world is so ill-defined. There is a need for better surveillance for vaccine-preventable pneumonia pathogens and improved methods of pathogen detection to guide a reinvigorated global program to prevent and control pneumonia.

These new opportunities demand renewed effort. Although pneumonia is a reportable disease in many countries, what is being reported is often not clear. Methods often include passive surveillance, non-standardized case definitions relying on clinical diagnosis, lack of radiographic confirmation, and lack of laboratory identification of pathogens, limiting the value of the data for use in guiding prevention and control programs.[5] In 2002, Thailand launched active, population-based surveillance for radiographically confirmed pneumonia as part of the International Emerging Infections Program (IEIP), a novel collaboration between the U.S. Centers for Disease Control and Prevention and the Thai Ministry of Public Health.[6]

Material and methods

Population

Sa Kaeo is a rural province located about 200 kilometers east of Bangkok on the border with Cambodia. In 2002, the average monthly household income was 9951 Baht (US$248.78) and the population is largely agrarian.[7] The population of Sa Kaeo, 438 557, was defined as the surveillance area. There is one provincial hospital, six community hospitals, and one military hospital. Since 1975, pneumonia surveillance has been a core function of the Thai Ministry of Public Health and as such has been determined not to require review by ethical committees or institutional review boards. In September 2002, the pneumonia surveillance system in Sa Kaeo was modified to include active case ascertainment at all eight hospitals in the province. There are no private or other acute care hospitals in the province, and therefore these hospitals capture essentially all of the acute care admissions for the population under surveillance. All hospitals are equipped with at least basic laboratory facilities and staffed by one or more university-trained laboratory technicians. Although routine microscopy, chemistry, hematology, and serologic testing are available, equipment and materials to conduct bacteriological testing is lacking or limited. There is universal health care and patients pay 30 Baht (US$0.75) per visit, but this fee is much less than the cost of a hospital stay.

Case definition

A case of clinical pneumonia was defined as evidence of acute infection (at least one of the following: reported fever or chills, documented temperature $>38.2\,^\circ\text{C}$ or $<35.5\,^\circ\text{C}$, white blood cell count $>11 \times 10^9/\text{L}$ or $<3 \times 10^9/\text{L}$ or abnormal differential) and signs or symptoms (at least one of the following: abnormal breath sounds on chest auscultation, tachypnea, cough, sputum production, hemoptysis, chest pain, or dyspnea) of lower respiratory tract disease in a resident of Sa Kaeo.[8] Radiographically confirmed pneumonia was defined as clinical pneumonia with evidence of an infiltrate on a chest radiograph taken within 48 hours of admission. Recurrent pneumonia was defined as two episodes of pneumonia separated by at least 14 days.

Information collection and flow

Surveillance officers prospectively reviewed hospital admission logs daily for patients admitted with a diagnosis that might suggest pneumonia (International Classification of Disease, version 10, codes A15–16, A19, A24, A37, B20, B22–24, B59, J10–22, J40, J45–46, J69, J80–81, J84, J90–91, J93–94, J96, J98, P22–26, R05–06, R09, R50). For each patient identified, the surveillance officer reviewed the medical chart for basic clinical, laboratory, and radiographic findings and completed a standardized surveillance form on patients who met the case definition. Physicians completed the section on clinical signs and symptoms. Laboratory data, such as normal ranges for white blood cell count, were generated by the hospital laboratories and interpreted by physicians. Patients were followed through until discharge so that information on complications, length of stay, and outcome could be captured. Surveillance forms were entered into a computerized database at each hospital and sent via a secure website to a server at the Ministry of Public Health.

Radiology

Radiographs were digitized using a Vidar SIERRA Plus film digitizer and sent to Bangkok for review by a panel of radiologists as per published protocol.[9] The readers, all board certified radiologists, were blinded to each other's readings and to all patient clinical and demographic data except age and sex. Two primary readers interpreted the radiographs and

a third served to resolve discrepancies. The radiologists used the WHO standard criteria for the interpretation of chest radiographs for diagnosing pneumonia in children.[10] In addition, a pilot study of 100 images was conducted so that all three readers could compare and standardize interpretations. Once the readings were completed data were merged with the surveillance database for analysis. A complete evaluation of digital compared to hard copy chest radiograph interpretations in this population has recently been published.[9]

Quality control/quality assessment

The surveillance coordinator and staff conducted data reviews at weekly staff and monthly provincial working group meetings. In addition, to ensure that all cases of diseases under surveillance were identified and reported, the Bureau of Epidemiology performed a complete and standardized data audit annually. The primary data source at every reporting site, the inpatient logbooks, was compared to the list of cases reported electronically for a one-month period to ascertain completeness of reporting. In addition, to evaluate coverage of the screening criteria, discharge data were reviewed to identify additional pneumonia patients and charts were reviewed to determine whether they met the case definition. Finally, the timing of all chest radiographs was monitored for the proportion that had a radiograph obtained within 48 hours, the criterion for inclusion.

Community survey

To ascertain health utilization patterns and estimate the proportion of all incidence pneumonia that presented to a hospital we conducted a community survey, the details of which are presented elsewhere.[11] In brief, 1600 households throughout the province were sampled using a two-stage cluster design, and household members were interviewed using a structured questionnaire. Self-reported pneumonia was defined as either cough with difficulty breathing for at least two days or being given a diagnosis of pneumonia by a healthcare provider.[12]

Statistical analysis

Descriptive data were summarized using frequencies (SPSS 11.0, SPSS Inc., Chicago, IL, USA). Proportions were compared and we report Fisher's exact 2-tailed p values; $p < 0.05$ was considered significant. To compare risk factors we computed relative risks (RR) and 95% confidence intervals (CI). Census data from the Sa Kaeo (2001) Provincial Health Offices were used to calculate the minimal incidence of pneumonia. To calculate the maximum incidence, rates were adjusted separately for each age category to account for incomplete chest radiography and health-seeking behavior using data from the community survey.[11] Specifically, in each age-group we multiplied the frequency of radiographically confirmed pneumonia by the total number of persons with clinical pneumonia and divided the result by the proportion that sought care. This number was then divided by the population to get an upper limit of the incidence. Data on routine service and ancillary costs associated with pneumonia hospitalization were collected in Sa Kaeo as part of another study.[13]

Results

Radiographically confirmed pneumonia

In Sa Kaeo between September 1, 2002 and August 31, 2003, there were 2775 episodes of clinical pneumonia requiring

Table 1   Clinical features of pneumonia episodes in Sa Kaeo, Thailand

Sign or symptom	Clinical pneumonia (N = 2775) n (%)	Clinical pneumonia with chest radiograph (N = 1064) n (%)	Clinical pneumonia with radiographic confirmation (N = 777) n (%)
Evidence of acute infection			
Reported or documented fever	2570 (93)	984 (93)	700 (90)
Reported or documented hypothermia	43 (2)	20 (2)	13 (2)
Leukocytosis (WBC >11 × 10^9/L)^a	1159 (42)	537 (51)	408 (53)
Leukopenia (WBC <3 × 10^9/L)^a	117 (4)	50 (5)	34 (4)
Abnormal WBC differential	756 (27)	278 (26)	195 (25)
Signs/symptoms of respiratory illness			
Cough	2657 (96)	1015 (95)	747 (96)
Sputum production	2079 (75)	892 (84)	661 (85)
Abnormal breath sounds	1555 (56)	743 (70)	579 (75)
Rales/crepitation or rhonchi	1220 (44)	642 (60)	511 (66)
Dyspnea	1390 (50)	653 (61)	506 (65)
Tachypnea	1269 (46)	636 (60)	494 (64)
Chest pain	506 (18)	283 (27)	220 (28)
Wheezing	628 (23)	273 (26)	210 (27)
Hemoptysis	94 (3)	62 (6)	51 (7)
≥3 Respiratory signs/symptoms	2020 (73)	919 (86)	705 (91)
Outcome			
Death	112 (4)	84 (8)	72 (9)

^{a} Age-specific cut-offs were used for children <5 years of age (The Harriet Lane Handbook. CV Mosby; 2002). WBC, white blood cell count.
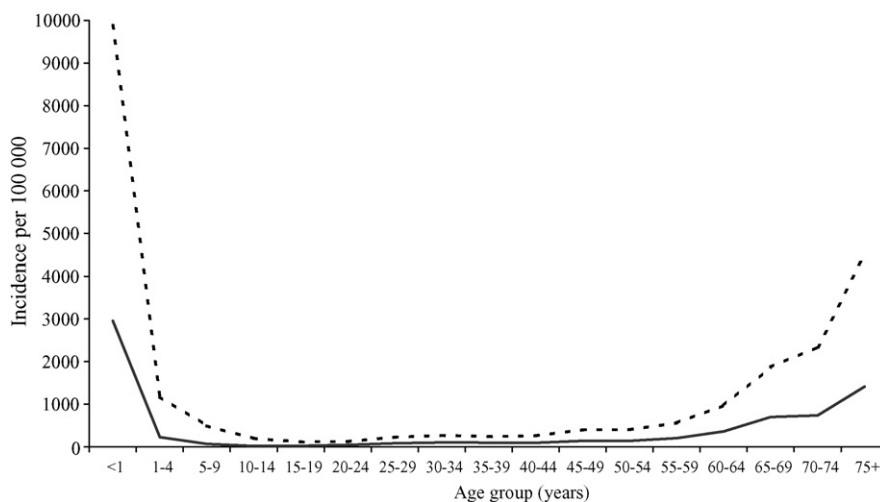
Figure 1 Incidence of radiographically confirmed pneumonia by age. The bold line is the measured incidence and the dotted line is the maximum incidence adjusted for complete ascertainment of chest radiographs and health-seeking behavior.

hospitalization and 1064 (38%) were in patients who had a chest radiograph. Persons aged 20 and older were significantly more likely to have a chest radiograph than those aged 0—19 (50% vs. 27%, respectively, RR = 2.7, 95% CI = 2.3—3.2). Persons who had a chest radiograph were also significantly more likely to die than those who did not (8% vs. 2%, RR = 5.1, 95% CI = 3.3—8.0). There was no difference in the proportion who were male (55% vs. 58%, RR = 0.9, 95% CI = 0.7—1.0). Of the 1064 who had a chest radiograph, 777 (73%) had radiographically confirmed pneumonia as assessed by the radiology panel. A comparison of the clinical presentation and outcome of these groups is presented in Table 1. Patients who had a chest radiograph closely resemble those with radiographically confirmed pneumonia. For the rest of the paper, we will describe the 777 episodes (in 754 persons) of radiographically confirmed pneumonia.

The incidence of radiographically confirmed pneumonia by age is shown in Figure 1. The minimal incidence, 177 per 100 000 per year, is the incidence based on the 777 confirmed cases and the maximum incidence, 580 per 100 000 per year, is the incidence after adjusting for incomplete chest radiography and access to health care (see community survey section below). Slightly more than half of the pneumonia cases

(424, 55%) were in men. There were six cases of pneumonia in neonates (age <1 month). Signs and symptoms at admission are reported in Table 1. The median length of hospital stay was 5 days (range 1—64); it was highest, at 7 days, in persons aged 30—34. The number of pneumonia cases appeared to peak twice during the year, once in January through March and then again in July through October (Figure 2).

The two primary readers agreed on the presence of a new infiltrate in 759 (98%) of the radiographs. Agreement between the two readers was slightly lower for the type of infiltrates (alveolar (609/777, 78%; kappa = 0.46) and interstitial infiltrates (608/777, 78%; kappa = 0.44)). Using the panel interpretation, the distribution of chest radiograph patterns was as follows: 341 (44%) alveolar, 424 (55%) interstitial pattern only, and 12 (2%) with other evidence of pneumonia such as pleural effusion or hyperaeration. Alveolar infiltrates were more common in persons with rales, crepitations, or rhonchi (47% vs. 38%, RR = 1.5, 95% CI = 1.1—2.0) or hemoptysis (63% vs. 44%, RR = 2.2, 95% CI = 1.2—3.9) or chest pain (51% vs. 41%, RR = 1.5, 95% CI = 1.1—2.1), whereas persons with wheezing were significantly more likely to have interstitial infiltrates (65% vs. 48%, RR = 2.0, 95% CI = 1.4—2.8).
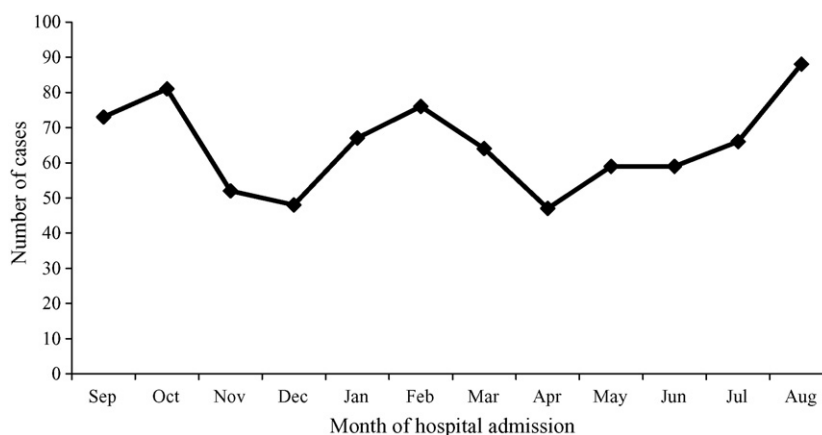

Figure 2 Number of radiographically confirmed pneumonia cases by month of hospital admission.
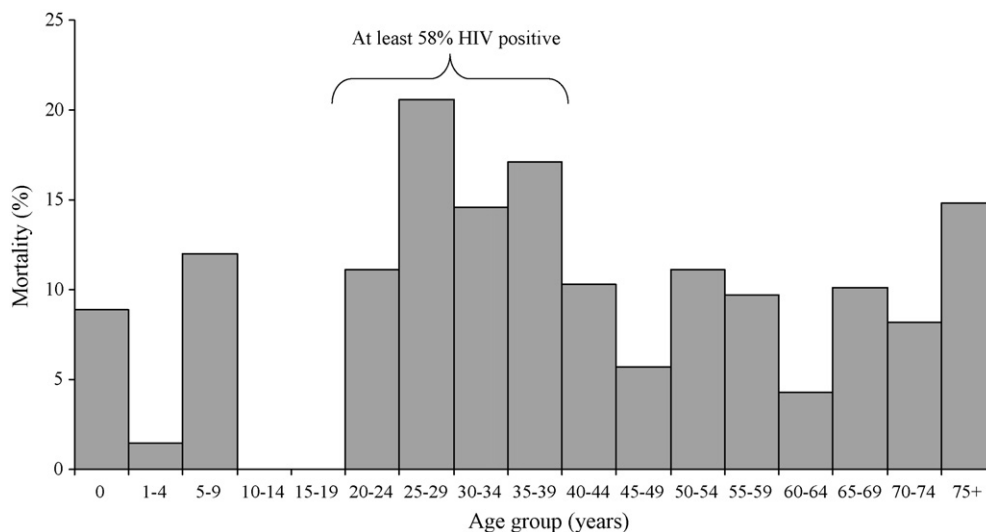
Figure 3 Mortality of radiographically confirmed pneumonia cases by age, Sa Kaeo, Thailand.

During hospitalization 227 (29%) patients were given supplemental oxygen and 45 of these persons required mechanical ventilation. Persons aged 65 and older were significantly more likely to require mechanical ventilation than persons of other ages (12% vs. 4%, respectively, RR = 3.1, 95% CI = 1.8—5.6). Twenty-one (3%) patients had thoracentesis and no pneumonectomies were reported. Seventy-two (9%) patients died and mortality did not differ between men and women, (8.9% vs. 9.6%, respectively, RR = 0.9, 95% CI = 0.6—1.4). Mortality was greatest in adults aged 25—40 (16%) and persons aged 75 and older (15%, Figure 3). Twenty (28%) of the persons who died were known to be HIV positive. Persons with HIV infection were significantly more likely to die than those without HIV infection (74% vs. 26%, RR = 4.4, 95% CI = 1.3—14.8).

Community survey

We surveyed 5658 persons in 1600 households.[11] A total of 62 (1%) persons met the case definition for pneumonia within the one-year recall period. Of the 59 persons with complete data, 53 (90%) sought medical care and 47 (80%) sought care at a hospital facility in the province. Children were more likely to be brought to a medical facility than adults. The age-specific frequency of health seeking at a hospital facility was as follows: 0—14 years, 86.5%; 15—64 years, 71.4%; and 65 and older, 62.5%. Neither distance from a medical facility nor cost was reported as a barrier to seeking care.

Laboratory findings

At admission, 411 (53%) had leukocytosis (WBC $>11 \times 10^9$/L) and 23 (3%) had leukopenia (WBC $<3 \times 10^9$/L). Sixty-five (8%) patients had a sputum culture, 35 cultures had normal respiratory flora, 23 grew *Klebsiella spp*, five *Burkholderia spp*, one *Staphylococcus aureus*, and one *Legionella spp*. Only 45 (6%) patients had a blood culture; two (4%) of these were positive, one each for *Staphylococcus aureus* and *Burkholderia spp*. Twenty-nine (4%) were known to be HIV seropositive. Two hundred and thirty-six (30%) patients had at least one sputum smear for acid-fast bacilli; 47 were positive (20%

of tested and 6% of all patients). Of the 47 positives, the median age was 41 years (range 15—84), 33 (70%) were male, and 11 (23%) were known to be HIV seropositive.

Recurrent pneumonia

Fifteen (2%) patients were admitted twice for pneumonia during the year. The median time between hospitalizations was 56 days (range 15 to 272). Two (13%) patients with recurrent pneumonia died, a 30-year old HIV-positive man and a 75-year old man diagnosed with TB. Both tuberculosis and HIV were common in patients with recurrent pneumonia; three (20%) were diagnosed with tuberculosis and two (13%) with HIV. Persons who had wheezing on presentation were significantly more likely than those who did not have wheezing to have recurrent pneumonia (4% vs. 1.3%, RR = 3.2, 95% CI = 1.2—8.6). There was no difference in sex or age.

Cost

At an average cost of routine service per hospital admission day of US$31.10 at a provincial hospital and US$28.08 at a district hospital, and an ancillary cost per pneumonia inpatient day of US$94.62, the average cost per pneumonia episode was US$628.60 at the provincial hospital and US$490.80 at the district hospital. For this one-year period, the total cost for pneumonia hospitalization in Sa Kaeo was US$653 881.62.

Discussion

The incidence of radiographically confirmed pneumonia requiring hospitalization in rural Thailand is high. Our estimates range from 1- to 3-fold higher than previous estimates based on passive surveillance.[5] Mortality from pneumonia has also been greatly underestimated, by approximately 11-fold. As shown here and elsewhere,[14,15] the population-based approach, although financially and human resource intensive, provides accurate measures of the burden of disease. Accurate estimates and ongoing monitoring of the incidence of pneumonia using international standards should form an

essential foundation for much needed renewal of efforts to reduce the burden of this leading cause of illness and death.

Although chest radiography remains the standard approach to confirming a pneumonia diagnosis worldwide, lack of equipment and expense often limit its use in less wealthy countries.[16] In our surveillance province, all hospitals had radiographic equipment and the Ministry of Public Health supplemented hospital funds to offset any additional costs of the film. Despite this, only 38% of suspected pneumonia patients had a chest radiograph, highlighting some of the challenges to accurately measuring the burden of pneumonia using radiographically confirmed cases alone. Given this limitation to pneumonia diagnosis in our study, it is likely that the true incidence of pneumonia lies between our minimum and maximum values.

This surveillance system aims to provide a comprehensive picture of severe, radiographically confirmed pneumonia that results in hospitalization. Recognizing that not all pneumonia patients may present to a hospital and if they do, not all have a chest radiograph, we adjusted our incidence figures accordingly. Access to health care is very good in Thailand; 80% of persons with self-reported pneumonia sought care at a hospital and thus have the opportunity to be captured in the surveillance system.[11] Compared with other tropical areas, most patients with pneumonia in a rural Thailand setting can get to the hospital and have a chest radiograph, and thus there was a relatively small (3-fold) difference between our measured incidence and the extrapolated total incidence. In other settings this difference might be greater, but the general approach should be applicable for generating more accurate estimates of pneumonia burden.

There has been little systematic study of the seasonality of respiratory pathogens in tropical climates. Our data on pneumonia suggest a possible seasonal pattern with a large peak in July through October and perhaps a smaller one in January through March. These two peaks were confirmed in preliminary unpublished data for the second year in Sa Kaeo and a second surveillance province, Nakhon Phanom, as well as the pattern seen in the past from passive surveillance.[5] The July through October peak coincides with the peak in clinically defined influenza-like illness (June through September) as well as influenza viral isolation (June through October).[17] Unfortunately, in rural Thailand hospitals infrequently identify the etiology of the pneumonias. Less than 10% of patients with radiologically confirmed pneumonia had a blood culture and viral testing is not available. As more information on the specific pathogens causing pneumonia is accumulated through this system, the underlying causes for the seasonal peaks should become apparent.

Since the late 1980s, reported pneumonia incidence and mortality have been increasing in Thailand, a troubling finding and one that may be related to the emerging HIV epidemic.[5] TB pneumonia is of particular concern in HIV-infected persons,[18] and Thailand is listed as one of the 22 high-burden TB countries in the world.[19] In our surveillance province, sputum smears for acid-fast bacilli were only performed in one third of cases, but these and physician diagnoses suggest that many of the patients with recurrent pneumonia may have had tuberculosis with or without HIV. Additional efforts, such as enhancing diagnostic services to include culture and sensitivity to more appropriately guide treatment, are needed to adequately address the substantial problem of tuberculosis in Thailand. In addition, HIV testing and counseling should be offered to all pneumonia patients, as the prevalence is likely higher than the 4% identified in this study. As in a study in rural Haiti, we found wheezing to be associated with recurrent pneumonia.[20] This highlights the potential importance of reactive airway disease, a clinical entity with effective treatment that remains relatively unexplored in tropical areas.

Thailand is a middle-income country with a relatively low infant mortality rate of 24 and under 5 mortality rate of 28 per 1000 live births.[21] Given its fairly advanced health state, it is unlikely that substantial reductions in the morbidity and mortality from pneumonia will result from the simple case management strategies advocated since the 1980s. As in developed countries, Thailand now needs to consider the introduction of new and existing vaccines effective against pneumonia pathogens. Comprehensive etiologic studies are already underway in the IEIP Thailand surveillance sites to quantifying the burden of vaccine-preventable diseases, such as influenza, *S. pneumoniae*, and *H. influenzae* type B. The systematic approach to monitor the burden of pneumonia in Sa Kaeo is adoptable for use in other settings.

Conflict of interest: No conflict of interest to declare.

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