Epidemiology of Community-Acquired Pneumonia Hospitalizations and Associated Complications Before and After the Implementation of the Heptavalent Pneumococcal Conjugate Vaccine in Athens, Greece

Theano Lagousi,1 Ioanna Papadatou,1 Ioannis Kopsidas,1 Elena Critselis,2 Maria Theodoridou,1 and Vana Spoulou1
1First University Department of Pediatrics, “Aghia Sophia” Children’s Hospital, National and Kapodistrian University of Athens School of Medicine, Greece; and 2The Stavros Niarchos Foundation—Collaborative Center for Clinical Epidemiology and Outcomes Research, First and Second University Departments of Pediatrics, National and Kapodistrian University of Athens School of Medicine, Greece

Corresponding Author: Vana Spoulou, MD, MPhil, PhD, First University Department of Pediatrics, “Aghia Sophia” Children’s Hospital, Thivon and Papadiamantopoulou str. Goudi, 11527, Athens, Greece. E-mail: vspoulou@med.uoa.gr.

We determined the rates of community-acquired pneumonia (CAP)–associated hospitalizations and complications in Athens, over a period covering 4 years before and 4 years after the implementation of the 7-valent pneumococcal vaccine (PCV7) in Greece. PCV7 had no impact on pediatric CAP rates, whereas there was an increase in CAP-associated complications.

Key words. children; pneumococcal vaccine; pneumonia.

INTRODUCTION
Community-acquired pneumonia (CAP) is the most common infection requiring hospitalization among pediatric populations in developed countries and the most common cause of childhood mortality in the developing world [1]. Streptococcus pneumoniae is the most commonly isolated bacterial pathogen of CAP in children [1].

The 7-valent pneumococcal conjugate vaccine (PCV7) resulted in an impressive decrease in invasive pneumococcal disease (IPD) not only in vaccinated children, but also in the unvaccinated population, due to vaccine-induced herd immunity [2]. However, the impact of PCV7 on CAP epidemiology is less clear, and controversy exists over its effect on CAP incidence [3, 4] and CAP-associated complications [5, 6].

The 13-valent formulation (PCV13) has recently replaced PCV7, aiming to target the residual burden of pneumococcal disease caused by non-PCV7 serotypes. PCV13 was licensed on the basis of noninferiority immunogenicity studies rather than clinical efficacy trials; thus, postlicensure monitoring is required to reveal potential changes based on baseline epidemiology of CAP and associated complications found in each country. In Greece, PCV7 was replaced by PCV13 at the end of 2010. The aim of this study was to compare admission rates for CAP and associated complications pre- and postintroduction of PCV7 and provide reliable baseline data on childhood CAP epidemiology of the pre-PCV13 era.

METHODS
We conducted an 8-year (2004—2011) retrospective pre–post study in a tertiary-care children’s hospital, “Aghia Sophia,” in Athens covering 4 years before and 4 years after the introduction of PCV7 in the National Immunization Program (NIP) in 2006. The pre-PCV7 period included the year 2006 in order to account for the uptake of the vaccine in the market. The local Hospital Ethics Review Board approved the study protocol. A waiver for informed consent was provided.
Study Population
All patients aged ≤14 years with CAP, admitted to “Aghia Sophia” Children’s Hospital during the period January 1, 2004–December 31, 2011, were included in the study. In Greece, pediatric hospitals admit children up to the age of 14 years; therefore, we could not extend our study group to all school-aged children. CAP cases were defined as “patients with discharge diagnosis of pneumonia, bronchopneumonia, and/or lower respiratory tract infection,” according to the electronic database of the hospital. Patients with an additional discharge diagnosis of parapneumonic pleural effusion, empyema, lung abscess (localized complications) and/or systemic inflammatory response syndrome/sepsis, hemolytic uremic syndrome, acute respiratory failure (systemic complications) were defined as complicated CAP cases. Since ICD-9 codes were not used systematically in the particular setting, the accuracy of discharge diagnosis was further validated with the review of approximately 10% of each year’s relevant medical records. All retrieved medical records that were checked manually confirmed the diagnosis of CAP. For all complicated cases, medical records were retrieved manually to specifically obtain detailed information on patients’ clinical characteristics, co-morbid conditions, causative agent of CAP, etc. Patients with co-morbid conditions (including malignancy, collagen vascular disease, sickle cell disease, cystic fibrosis, organ transplantation, congenital heart defects, and heart failure) and trauma were excluded from the study. Children with asthma or recurrent wheezing were not excluded from our study population.

PCV7 vaccination history was evaluated in details based on information recorded in medical records of each patient with complicated CAP. We defined as fully vaccinated children those who had received 3 or more doses of PCV7 and as partially vaccinated those children who had received 1–2 doses. For the rest of the CAP cases, PCV7 vaccination status was only assumed according to their age. Children older than 5 years were assumed to be unvaccinated because following the implementation of PCV7 in 2006, there was no catchup program.

Statistical Analysis
Categorical variables are expressed as frequencies and percent. Time trends in the occurrence of total CAP and complicated CAP admissions were assessed with time series analysis (ARIMA modeling procedure). Time series analyses were also conducted within stratified age groups. Analyses were undertaken with the SPSS v. 17.0. P < .05 was considered the criterion of significance.

RESULTS
Overall, there were 103,407 hospital admissions in children aged ≤14 years, and CAP admissions accounted for approximately 2.4% (n = 2504) of them. The proportion of CAP-associated hospital admissions in 2011 was 2 times greater than in 2004 and was observed mainly among children aged >5 years assumed to be PCV-7 naïve according to the Greek NIP. CAP admission rates remained stable in infants and children aged 1–4 years old. During the study period, the annual incidence of total hospital admission as well as the incidence of hospitalization for other conditions (eg, appendicitis) and intensive care unit (ICU) admission that would be susceptible to health system changes and economic challenges in Greece remained relatively stable (Table 1).

Among all study patients, 5.5% (n = 138) had complicated CAP. Complicated CAP admissions increased by approximately twofold during the study period. The overall admission rate for complicated CAP cases rose from 3.5% in 2004 to 6.9% in 2011 (P = .007). This increase was

Table 1: Time Trends in Pediatric Total Community-Acquired Pneumonia (CAP) Admissions and Complicated CAP Admissions According to Age

| Year   | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | P
|--------|------|------|------|------|------|------|------|------|---
| Total hospital admissions, n | 11687 | 12715 | 13640 | 13871 | 14236 | 14006 | 12712 | 10540 | 0.703
| Total appendicitis admissions, n (%) | 80 (0.7) | 91 (0.7) | 55 (0.4) | 64 (0.5) | 62 (0.4) | 15 (0.1) | 77 (0.6) | 252 (2.4) | 0.288
| Total ICU admissions, n (%) | 309 (2.6) | 300 (2.4) | 261 (1.9) | 172 (1.3) | 187 (1.3) | 263 (1.9) | 229 (1.8) | 264 (2.3) | 0.628
| Total CAP admissions, n (%) | 255 (2.2) | 310 (2.4) | 234 (1.7) | 280 (2.0) | 286 (2.0) | 309 (2.2) | 367 (2.9) | 463 (4.4) | 0.020
| Infants aged <1 y, n (%) | 16 (6.3) | 20 (6.4) | 20 (8.5) | 11 (3.9) | 21 (7.3) | 18 (5.8) | 16 (4.4) | 24 (5.2) | 0.486
| Toddlers aged 1–4 y, n (%) | 119 (46.7) | 129 (41.6) | 96 (41.0) | 108 (38.6) | 112 (39.2) | 114 (36.9) | 141 (38.4) | 129 (27.9) | 0.356
| Children aged 5–9 y, n (%) | 100 (39.2) | 121 (39.0) | 90 (38.5) | 113 (40.4) | 128 (44.8) | 120 (38.8) | 156 (42.5) | 246 (53.1) | 0.025
| Children aged >9 y, n (%) | 20 (7.8) | 40 (12.9) | 28 (12.0) | 47 (16.8) | 25 (8.7) | 57 (18.4) | 54 (14.7) | 64 (13.8) | 0.019
| Total complicated CAP admissions, n (%) | 9 (3.5) | 7 (2.2) | 8 (3.4) | 24 (8.6) | 13 (4.5) | 23 (7.4) | 22 (6.0) | 32 (6.9) | 0.007
| Infants aged <1 y, n (%) | 1 (11.1) | 0 (0.0) | 0 (0.0) | 1 (4.2) | 1 (7.7) | 2 (8.7) | 4 (18.2) | 5 (15.6) | 0.006
| Toddlers aged 1–4 y, n (%) | 33 (33.3) | 45 (57.1) | 4 (50.0) | 4 (50.0) | 7 (29.2) | 8 (31.0) | 10 (43.5) | 9 (40.9) | 0.001
| Children aged 5–9 y, n (%) | 4 (44.4) | 2 (28.6) | 3 (37.5) | 11 (45.8) | 23 (91.1) | 7 (30.4) | 8 (36.4) | 12 (37.5) | 0.063
| Children aged >9 y, n (%) | 1 (11.1) | 1 (14.3) | 1 (12.5) | 5 (20.8) | 1 (7.7) | 4 (17.4) | 1 (4.5) | 6 (18.8) | 0.163

P < 0.05, which was considered the criterion of significance, is presented in bold/italics.
Abbreviation: ICU, intensive care unit.

Percent of total hospital admissions.
Percent of total CAP admissions.
observed mainly in infants and children aged <4 years, whereas it remained unchanged in older children (Table). Among complicated CAP patients, 134 (97.1%) had localized complications; 85 (63.4%) patients presented with pleural effusion, 23 (17.2%) with empyema, 14 (10.4%), with abscess and 12 (9%) with necrotizing pneumonia. An increasing trend over time for the occurrence of empyema among complicated CAP cases was documented ($P = .131$). Among complicated CAP cases, only 4 patients presented with systemic complications (including 2 cases of septicemia, 1 case of septic shock and multiorgan failure, and 1 case of hemolytic uremic syndrome). It is noteworthy that 82% ($n = 110$) of localized complications and all systemic complications were observed in patients hospitalized for complicated CAP in the post-PCV7 era.

A limited proportion (10.1%) of patients with complicated CAP were recent immigrants, and thus differences in CAP epidemiology or PCV7 immunization program of their homeland are less likely to have influenced rates of complicated CAP. Moreover, 66.7% of complicated CAP cases had previously received antibiotics. Approximately two-thirds ($n = 95$) of patients with complicated CAP were fully ($n = 59$) or partially ($n = 46$) vaccinated with the PCV7. Although 7.2% of patients with complicated CAP had a positive history for recurrent wheezing or asthma, the potential confounding effect of asthma upon recurrent and more severe cases of pneumonia could not be assessed due to inadequate sample size. In 33 (24%) of complicated CAP cases in which the etiological agent was identified, $S$ pneumoniae accounted for nearly half of them (5 vs. 10 in the pre- vs. post-PCV7 era), followed by *Staphylococcus aureus* (2 vs. 8), b-hemolytic *Streptococcus* Group A (1 vs. 2), *Enterobacter* (2 vs. 2), and *Klebsiella* (0 vs. 1). Remarkably, methicillin-resistant *S aureus* (MRSA) was identified in only 2 complicated cases. Over time, complicated CAP cases were increasingly found to necessitate ICU admission ($P = .008$), although the rate of overall ICU admissions during the study period did not significantly change ($P = .0628$). During the study period, ICU admission was mostly related to chest tube insertion/drainage or chest surgery, while none of the children was intubated.

**DISCUSSION**

We found that CAP remains an important cause of childhood admissions in Athens, Greece. PCV7 had no impact on CAP rates among children assumed to be fully or partially vaccinated, and there was an increase in CAP-associated complications.

CAP rates remained unchanged in infants and children up to 5 years of age, whereas an approximately twofold increase was observed in children older than 5 years throughout the study period, while total hospital admissions remained stable. Most children aged ≤5 years were assumed to be fully or partially vaccinated. This is supported by recently published data by the Hellenic center for prevention and disease control (KEELPNO) national vaccination coverage data, reporting 94% PCV7 vaccination coverage in Greece (http://www.keelpno.gr). Children older than 5 years were assumed to be unvaccinated due to the lack of a catchup program for older children when PCV7 was first implemented in Greece. Our findings of no PCV7 impact on CAP rates among young children contrast with previous reports demonstrating a reduction in CAP hospital admissions among vaccinated children, especially those aged <1 year [4]. Furthermore, the increase in CAP admissions found in unvaccinated older children is in contrast with reports showing reduced rates of CAP among unvaccinated populations due to herd immunity [2]. Such differences could be partially attributed to the increase of viral pneumonias occurring during the 2009–2010 H1N1 pandemic [7], although similar trends persisted also in the following year. All patients were accurately diagnosed with CAP based on the review of the 10% sample, supporting our contention that most of the patients in the study likely had CAP. Importantly, the possibility that our data have been influenced by health system changes and economic challenges in Greece, affecting pneumonia prevalence related to delays in bringing children to medical attention or changes in catchment or referral area, is less likely since other hospital admission rates checked remained unchanged during the study period.

The observed increasing trend over time for the occurrence of complicated CAP is in accordance with other reports showing similar increase, which has been potentially associated with the emergence of virulent non-PCV7 serotypes [6, 8]. Local epidemiological data have confirmed a noticeable replacement of PCV7 serotypes by nonvaccine serotypes in terms of colonization and acute otitis media in Greece [9], and there is increasing evidence of a relation between nasopharyngeal colonization and pneumococcal disease [10]. Therefore, we can assume that colonizing nonvaccine serotypes could be partly associated with the observed increase in complicated CAP. We found no evidence of other factors that could be associated with the observed increase in complicated CAP cases (eg, the spread of community-acquired MRSA, which accounted only for 2 of 10 staphylococcal cases) or the emergence of multidrug-resistant strains in Greece, which account for only 5.1% of serotypes causing IPD [11].

Although our study was held at a single center, it is important to note that the study site is the largest Children’s
Hospital in Greece serving as a national referral pediatric hospital. Although our study was not based on ICD-9 codes for discharge diagnosis, the review of the 10% sample revealed that all patients had CAP, suggesting that no misclassifications have been determined. Moreover, although the identification of associated complications could have been under- or overestimated due to inaccuracy of discharge diagnosis, we presume that such misclassifications would not have occurred disproportionally from 1 year to the other, and thus the observed trends are more likely to represent true trends. Subanalyses of patients with asthma could not be conducted due to limited sample size and availability of robust data.

In conclusion, our findings show that at a pediatric tertiary-care environment, CAP is responsible for significant childhood morbidity before and after the implementation of PCV7. PCV13 has been launched in the NIP at the end of 2010 and is expected to reduce CAP and associated complications not only because it offers broader coverage including serotypes with increased virulence capacity, but also because the emerging serotypes will possibly have reduced potential for invasive disease due to the low case-to-carrier ratios they demonstrate [12]. Amidst a period of financial difficulties for many European countries, the effect of PCV13 upon the evolution of epidemiology of pneumococcal disease and all-cause CAP requires continuous monitoring. Our findings provide reliable baseline data that could be used for the prospective assessment of PCV13 effect on CAP epidemiology in Greece.

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REFERENCES