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# Impact of PCV7/PCV13 introduction on community-acquired alveolar pneumonia in children <5 years

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ABSTRACT

*Background:* Alveolar community-acquired pneumonia (A-CAP) is mostly considered a bacterial disease, mainly pneumococcal. This study was conducted to document the impact of sequential 7-valent and the 13-valent pneumococcal conjugate vaccines (PCV7; PCV13) on emergency room and hospitalization for A-CAP among children <5 years of age.

*Methods:* This is an ongoing prospective population-based study in southern Israel. The current analysis spans over the period July 2002 through June 2013. A-CAP was defined using the World Health Organization (WHO)'s criteria for radiologically-confirmed pneumonia. PCV7 was introduced in Israel in July 2009 and gradually replaced by PCV13 in November 2010. Pneumococcal conjugate vaccine (PCV) impact was calculated by comparing incidences during 3 pre-defined periods: pre-PCV (2002–2008), PCV7 (2010–2011) and PCV13 (2012–2013).

*Results:* Overall, 10,142 A-CAP episodes occurred. The annual incidences (per 1,000 inhabitants) in children <5 years old declined from a mean (±standard deviation) of 13.8 ± 0.9 in the pre-PCV period to 11.2 ± 2.7 in the PCV7 period and 7.4 in the PCV13 period, representing a reduction of 13% and 47%, respectively. The overall decrease was significantly faster among outpatients than among hospitalized children (42% and −8%, respectively in the PCV7 period; 68% *vs.* 32% in hospitalized children in the PCV13 period). While in children 12–23 months a significant decline was observed during the PCV7 and PCV13 periods, significant declines in A-CAP rates were observed only during the PCV13 period in the <12 months and 24–59 months age groups (44% and 46%, respectively).

*Conclusions:* A moderate decline in hospital A-CAP visits in children <5 years old was observed after PCV7 introduction. In contrast, after PCV13 introduction a substantial reduction in all visits was evident.



## 1. Introduction

The introduction of the 7-valent and the 13-valent pneumococcal conjugate vaccines (PCV7 and PCV13) to the National Immunization Plan (NIP) in many countries, including Israel, resulted in major reductions in invasive pneumococcal disease (IPD) [1–3], pneumonia [4–7] otitis media [8], and pneumococcal carriage [9] in children.

Radiographically confirmed alveolar pneumonia, as defined by the World Health Organization (WHO), is considered most often a bacterial disease and served therefore as an endpoint for vaccine efficacy studies in several pivotal pneumococcal conjugate vaccine (PCV) pre-licensure studies [10]. In these studies, the efficacy ranged from 20% to 37% in infants and young toddlers [11–16].

Although several post-PCV7 implementation studies reported vaccine impact on pneumonia, differences in case definition and methodology were significant [4,7,17–21]. Since the 10-valent pneumococcal conjugate vaccine (PCV10) and PCV13 were only recently introduced, only a limited number of impact data are available for these vaccines [22,23].

In southern Israel, >95% of the children are born at the only medical center in the region, where they also receive medical

*Abbreviations:* A-CAP, alveolar community-acquired pneumonia; PCV7, 7-valent pneumococcal vaccine; PCV10, 10-valent pneumococcal vaccine; PCV13, 13-valent pneumococcal vaccine; WHO, World Health Organization; PCV, pneumococcal conjugate vaccine; NIP, National Immunization Plan; IPD, invasive pneumococcal disease; PER, pediatric emergency room; SUMC, Soroka University Medical Center; Hib, *Haemophilus influenzae* b; IRR, incidence rate ratios; CI, confidence intervals.

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treatment, enabling prospective population-based studies. PCV7 was introduced to the Israeli NIP in July 2009 (with a catch-up immunization plan) and has been gradually replaced by PCV13 since November 2010, without a catch-up program. This sequential PCV7/PCV13 introduction, together with the unique epidemiological situation in southern Israel, provided the opportunity to observe the impact of these vaccines on hospital pediatric emergency room (PER) visits and hospitalization due to radiologically-confirmed alveolar community-acquired pneumonia (A-CAP).

We recently reported a substantial reduction of bacteremic pneumococcal pneumonia after the introduction of the sequential PCV7/PCV13 program in children <5 years old, using a prospective active nationwide surveillance [24]. However, since in young children only <10% of all pneumonia cases are bacteremic [25–27], there is a need to study incidence dynamics of all, mostly non bacteremic, alveolar pneumonia after PCV introduction in this age group. Since 2002, a prospective ongoing study is being conducted in southern Israel, in which all PER visits and hospitalizations due to radiologically-proven A-CAP are being recorded. The aims of the current study were: (1) To document the impact of the sequential PCV7/PCV13 introduction on hospital visits and hospitalizations due to A-CAP in young children; and (2) To assess whether the pattern of reduction in A-CAP rates was similar in hospitalized children and outpatients seen at the PER.

## 2. Materials and methods

### 2.1. Setting

The Soroka University Medical Center (SUMC) is the only hospital in the Negev district of southern Israel, providing primary and referral health services to the entire population of the region (>643,000 inhabitants and 77,000 children under 5 years old in 2012) [28]. Over 95% of the children living in the region are served by the SUMC,enabling incidence figures calculations. Two ethnic populations reside in Southern Israel: The Bedouin Muslim population, resembling a developing population and in transition from a semi-nomadic to a urban lifestyle, and the Jewish population whose lifestyle is similar to that of a developed population [28,29]. The proportion of children born at the SUMC in each ethnic group during the study period is approximately equal: 7507 Jewish children and 7174 Bedouin children [28]. Hospitalization rates for respiratory infectious diseases and especially for A-CAP are higher among the Bedouin population [27,28]. As medical insurance for children in Israel is universal and free of charge, there are no financial barriers for health-care service use in the region. The study was approved by the Institutional Ethics Committees of the SUMC. In Israel, *Haemophilus influenzae b* (Hib) vaccine has been included in the NIP since 1994 with >95% coverage and an impact exceeding 95% [30].

### 2.2. Vaccine uptake

Estimates of PCV7 coverage before 2009 were based on sales figures provided by the distributor. In 2007–2008, the proportion of 12–23 month old Jewish and Bedouin children who had received ≥2 PCV doses were ∼25% and <5%, respectively. The methodology of evaluating vaccine uptake has been described elsewhere [2]. In June 2009, 2010, 2011, 2012 and 2013, the proportion of 7–11 month old children who had received ≥2 doses of any PCV was 18%, 81%, 90%, 89% and 89%, respectively. The respective figures for PCV13 were 1%, 3%, 30%, 86% and 89%. The PCV13 vaccine is not being used routinely in the elderly population in Israel.

### 2.3. Study design

This is an ongoing, prospective, population-based, observational study, initiated in July 2002. The analysis in the current article was performed using data from July 2002 through June 2013. Data on annual numbers of children under 5 years of age living in the Negev region of Southern Israel were obtained from the Central Bureau of Statistics [28]. All children <5 years old visiting the SUMC pediatric emergency room with radiologically-proven A-CAP were included. This included both children who were hospitalized and those who were subsequently discharged from the emergency department without hospitalization (defined as outpatients).

Children from whom A-CAP was diagnosed ≥48 h from hospital admission were excluded since our aim was to study community-acquired episodes only.

### 2.4. Case definition

A patient was enrolled if all of the following criteria were fulfilled: (1) Age <60 months; (2) a resident of the Negev region; (3) the child was diagnosed radiologically as having A-CAP according to the WHO definitions [10].

A new pneumonia episode was defined as radiologically confirmed pneumonia which occurred >28 days following the diagnosis of a previous pneumonia episode.

### 2.5. Chest radiograph analysis

In >80% of the cases, both antero-posterior and lateral chest radiographs were obtained and read. All chest radiographs were analyzed as described previously [31]. Briefly, chest radiographs were analyzed according to the WHO Standardization of Interpretation of Chest Radiographs Working Group, using the following definition for alveolar pneumonia: a dense opacity that may be a fluffy consolidation of a portion, whole of a lobe or of the entire lung, often containing air bronchogram and sometimes associated with pleural effusion [10].

Chest radiographs were performed according to the treating physician's request when pneumonia was suspected, and unrelatedly to the study protocol. In our hospital chest radiographs are being performed routinely in cases where pneumonia is suspected. All chest radiographs were collected daily and were evaluated separately by 2 pediatric infectious disease specialists (D. G. and R. D.) who read all the chest radiographs independently. Further analysis was performed by an independent pediatric radiologist (J.B-Z) who was unaware of the clinical data and the pediatricians' analysis. The presence of radiologically diagnosed A-CAP was confirmed by agreement of at least one of the study pediatric infectious disease specialists and the study pediatric radiologist.

### 2.6. Data collection

Detailed demographic, clinical and laboratory data were collected from the medical files and missing information was obtained by interviewing the parents or the child's primary care physician. The variables studied included gestational age, age at the time of A-CAP diagnosis, gender, ethnic origin (Jewish or Bedouin), site of hospitalization (pediatric wards or pediatric intensive care unit), clinical and laboratory characteristics and mortality. Polymerase chain reaction was not used for the detection of *Streptococcus pneumoniae* from blood or any sterile sites during the study.

### 2.7. Statistical analysis

Data were recorded using the Access Microsoft office software. Statistical analysis was performed using the SPSS 21.0 software.

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