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

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A B S T R A C T

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 care. The change in the incidence of A-CAP was studied.
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 was ~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 unrelatively 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.
Contingency table analysis measuring the association between cases and controls was conducted using Pearson χ² tests or Fisher exact test.

Annual incidence rates were calculated as the number of A-CAP divided by the total population at risk during each year of the study. The age-specific population at risk was estimated according to the Israeli Central Bureau of Statistics reports for the relevant years. Incidence rate ratios (IRR) and 95% Confidence Intervals (CI) were calculated for overall A-CAP incidences and for age specific groups comparing the 3 defined periods. IRRs were calculated using actual (absolute) numbers of extrapolated cases and population at risk. For the pre-PCV period mean numbers of cases and population at risk were used.

To determine the impact of the sequential PCV7/PCV13 introduction on the incidence of hospital visits and hospitalizations, we compared incidences during 3 pre-determined periods: (1) Pre-PCV period (July 2002–June 2008); (2) PCV7 period (July 2010–June 2011, when >70% of children 7–11 months old were vaccinated with ≥2 PCV7 doses, but not with PCV13); (3) PCV13 period (July 2012–June 2013, when >70% of 7–11 months olds were vaccinated with ≥2 PCV13 dose). However, continuous graphs with monthly incidences are presented from July 2002 through December 2013. To evaluate changes in incidence of hospital visits with A-CAP, we used full years (each year, July through June). Vaccine impact was calculated by incidence rate ratios (IRRs) and 95% CIs comparing the 3 periods, adjusted for ethnic group, hospitalization and age, when appropriate.

3. Results

From July 2002 through June 2013, a total of 70,483 chest radiographs were obtained in children <5 years, and in 10,142 (14.4%), an A-CAP episode was diagnosed. Of all A-CAP episodes, 7,464 occurred in the study-defined pre-PCV, PCV7 and PCV13 periods, and were used for comparison of incidence between these periods; of these, 4,570 (61.2%) were in hospitalized children, and 2,894 (38.8%) in outpatients.

Of the 10,142 episodes, blood cultures were obtained in 6,855 (67.6%) and only 200 (0.3%) were positive. Of these, 77 (38.5%) were positive for S. pneumoniae. The most common serotypes were 1 and 5: 22 (28.6%) and 12 (15.6%) isolates, respectively.

The mean overall age (± standard deviation) was 20.8 ± 15.7 months, with no significant differences between the 3 periods. There were 4,138 (55.4%) males, with no significant difference between periods. Of all A-CAP episodes, 4,485 (60.1%) and 2,973 (39.8%) occurred in Bedouin and Jewish children, respectively, with a significant higher proportion of Bedouins mainly in the PCV13 period (P = 0.006). In the pre-PCV period, 58.2% were hospitalized while in the PCV7 period and in the PCV13 period, 72.1% and 74.7% were hospitalized, respectively (Table 1).

Compared with the pre-PCV period, annual incidences in children <5 years of age declined by 13% and 47% in the PCV7 and PCV13 periods, from 13.8 ± 0.9 in the pre-PCV to 11.2 ± 2.7 in the PCV7 period and to 7.4 in the PCV13 period, respectively (Table 2 and Fig. 1). Significant reductions were observed in the total number of episodes <5 years of age, when the PCV13 period was compared to the pre-PCV period (Table 2 and Fig. 2) with no significant differences between the 3 age groups. However, the reduction dynamics differed between the age groups: While in children 12–23 months a significant 30% decline was already observed during the PCV7 period, (with a further 22% decrease in the PCV13 period), no significant declines in A-CAP rates were observed during the PCV7 period in the <12 months and 24–59 months age groups. However, for both age groups, a significant decline (44% and 46%, respectively) was observed when the PCV13 was compared to the pre-PCV period.

Compared with the pre-PCV period, the incidence rate ratios (IRR) in Jewish children <5 years of age declined by 17% (IRR: 0.83 [0.54–1.11]) and 54% (IRR: 0.46 [0.09–0.93]), and in Bedouin children <10% (IRR: 0.9 [0.67–1.12] and 42% (IRR: 0.58 [0.22–0.95]) in the PCV7 and PCV13 periods, respectively.

The dynamics in post-vaccination decline differed between hospitalized children and outpatients (Fig. 3 and Table 2): A close linear reduction throughout the post PCV7/13 introduction could be observed among outpatients (an overall 68% reduction with 42% reduction from the pre-PCVs to the PCV7 period and an additional 44% reduction from PCV7 to PCV13 period). In contrast, no reduction was observed in hospitalization rates in the PCV7 period compared to the pre-PCV period (showing a non-significant 8% increase), but a significant 36% reduction was seen from the PCV7 to the PCV13 period. The overall decrease was significantly more marked among outpatients than among hospitalized children (68% vs. 32%; P < 0.001).

The dichotomy between outpatients and hospitalized children was observed in all 3 age groups.

4. Discussion

The present population-based prospective study demonstrates, in spite of only a modest reduction of 13% in A-CAP in young children shortly after PCV7, a sharp decline of 47% shortly after PCV13 introduction. The initial reduction in A-CAP rate in the PCV7 period was mainly observed in outpatients and was more marked in children 12–23 months of age, but in the PCV13 period the rates declined significantly in all age groups, in both inpatients and outpatients. Still, the reduction among outpatient episodes was significantly higher than that among inpatients.

Previous reports examining PCV impact on pneumonia from different geographical sites were inconsistent because of considerable variations between the vaccine used (PCV7, PCV10, PCV11, PCV13), endpoints chosen, populations studied, and methodological key points. However, all showed impact on pneumonia (either

Table 1

<table>
<thead>
<tr>
<th>Age, months (mean ± SD)</th>
<th>Pre-PCV7 period (n = 5955)</th>
<th>PCV7 period (n = 919)</th>
<th>PCV13 period (n = 584)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12–23–n (%)</td>
<td>20.8 ± 15.5</td>
<td>20.4 ± 16.5</td>
<td>20.8 ± 16.5</td>
<td>Not significant</td>
</tr>
<tr>
<td>24–59–n (%)</td>
<td>21.88 (35.9%)</td>
<td>373 (40.6%)</td>
<td>227 (38.5%)</td>
<td>α = 0.007</td>
</tr>
<tr>
<td>Males–n (%)</td>
<td>1735 (29.1%)</td>
<td>220 (23.9%)</td>
<td>156 (26.4%)</td>
<td>α = 0.001</td>
</tr>
<tr>
<td>Jewish children–n (%)</td>
<td>2082 (27.9%)</td>
<td>326 (35.3%)</td>
<td>207 (35.1%)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Bedouin children–n (%)</td>
<td>3294 (55.3%)</td>
<td>522 (56.8%)</td>
<td>322 (54.6%)</td>
<td>γ = 0.001</td>
</tr>
<tr>
<td>Episodes occurring from November through March–n (%)</td>
<td>3745 (62.9%)</td>
<td>629 (68.4%)</td>
<td>379 (64.2%)</td>
<td>α = 0.001</td>
</tr>
<tr>
<td>Hospitalized–n (%)</td>
<td>3466 (58.2%)</td>
<td>663 (72.1%)</td>
<td>441 (74.7%)</td>
<td>α = 0.001; γ = 0.001</td>
</tr>
</tbody>
</table>
Table 2

Incidences (per 1000 children) and IRR of PER visits and hospitalizations for A-CAP in children <5 years and during the 3 pre-defined periods: Pre-PCV (July 2002–June 2008), PCV7 period (July 2010–June 2011) and PCV13 period (July 2012–June 2013).

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Mean annual incidencea Pre-PCVs period (±SD)</th>
<th>Annual incidence PCV7 Period</th>
<th>IRR (95% CI) PCV7 vs. pre-PCVs</th>
<th>Annual incidence PCV13 Period</th>
<th>IRR (95% CI) PCV13 vs. PCV7</th>
<th>IRR (95% CI) PCV13 vs. pre-PCVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall &lt;60</td>
<td>5.8 ± 0.6</td>
<td>3.4</td>
<td>0.58 (0.53–0.62)</td>
<td>1.9</td>
<td>0.56 (0.46–0.66)</td>
<td>0.32 (0.27–0.39)</td>
</tr>
<tr>
<td>&lt;12</td>
<td>5.8 ± 1.1</td>
<td>3.3</td>
<td>0.57 (0.41–0.81)</td>
<td>1.4</td>
<td>0.42 (0.26–0.68)</td>
<td>0.41 (0.28–0.60)</td>
</tr>
<tr>
<td>12–23</td>
<td>10.2 ± 1.2</td>
<td>4.8</td>
<td>0.47 (0.36–0.63)</td>
<td>3.2</td>
<td>0.66 (0.47–0.94)</td>
<td>0.31 (0.23–0.43)</td>
</tr>
<tr>
<td>24–59</td>
<td>4.4 ± 0.7</td>
<td>2.9</td>
<td>0.66 (0.53–0.83)</td>
<td>1.6</td>
<td>0.56 (0.42–0.75)</td>
<td>0.37 (0.28–0.48)</td>
</tr>
<tr>
<td>Hospitalized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall &lt;60</td>
<td>8.1 ± 0.6</td>
<td>8.7</td>
<td>1.08 (0.96–1.20)</td>
<td>5.6</td>
<td>0.64 (0.56–0.72)</td>
<td>0.68 (0.61–0.78)</td>
</tr>
<tr>
<td>&lt;12</td>
<td>18.7 ± 1.5</td>
<td>20.2</td>
<td>1.08 (0.92–1.27)</td>
<td>12.5</td>
<td>0.62 (0.52–0.74)</td>
<td>0.66 (0.55–0.79)</td>
</tr>
<tr>
<td>12–23</td>
<td>9.9 ± 1.1</td>
<td>9.3</td>
<td>0.93 (0.75–1.18)</td>
<td>6.6</td>
<td>0.70 (0.55–0.90)</td>
<td>0.66 (0.51–0.85)</td>
</tr>
<tr>
<td>24–59</td>
<td>3.9 ± 0.6</td>
<td>4.4</td>
<td>1.15 (0.93–1.41)</td>
<td>2.8</td>
<td>0.64 (0.51–0.79)</td>
<td>0.73 (0.58–0.92)</td>
</tr>
</tbody>
</table>

IRR: incidence rate ratio; 95% CI: 95% confidence interval.

IRRs are adjusted for age (when overall children<5 years are analyzed) and for ethnicity.

a Incidences per 1000 population.

b Number in parenthesis represent 95% CI.

pre-introduction efficacy or post introduction impact) [4-6,18,22,23]. For example, in studies using ICD-9 or ICD-10 codes as case definitions [4,18], reductions of ∼40% in CAP cases in children <24 months old were reported following PCV7 introduction. Similarly, PCV10 introduction in Brazil resulted in up to 30% reduction of all-cause pneumonia hospitalization cases in children <24 months [22], and in Uruguay, the introduction of PCV13 following PCV7 resulted in a 44.9% reduction in CAP cases in children 12–24 months [23]. In the UK, PCV7 introduction resulted in a 19% reduction of WHO-defined radiologically defined CAP rate in children <5 years, with reductions of 33.1% and 38.1% in overall and hospitalization rates, respectively, in children <2 years. [7].

Pneumococcal vaccines can serve as “vaccine probes” and hint toward the most common serotypes in pneumococcal related disease such as A-CAP, when etiology is difficult to determine. Thus, the observed reduction in our study, mainly after PCV13

Fig. 1. Monthly and annual rates (per 1000 children) of hospital visits for A-CAP in children <5 years, July 2002 through 2013.
introduction, strongly suggests the importance of the 5 additional PCV13 serotypes 1, 3, 5, 7F and 19A. This is consistent with some of our previous findings. In a study conducted in southern Israel before PCV introduction, we reported increased carriage prevalence of serotypes 1, 5, 7F and 19A in young children presenting with A-CAP, compared to those in healthy children [31]. Moreover, in this carriage study, serotype-specific different carriage rates were found to be related to age. The additional PCV13 serotypes such as 1, 5, and 7F were found more commonly after the age of 24 months while serotypes 14 and 19A were found more commonly in the younger age group. This might explain the differences in the reduction of CAP in children younger than 24 months compared to older children. This suggested a high disease potential of the additional PCV13 serotypes. Furthermore, a recent nationwide study in Israel showed that in children with bacteremic CAP, serotypes 1, 5 and 19A predominated, resulting in a profound reduction of bacteremic CAP rates following the introduction of PCV13 [24,32,33], in the presence of only a mild reduction during the PCV7 period. Those findings were strikingly similar to the findings in the current study on non-bacteremic cases. This strongly suggests similarity between serotypes causing bacteremic pneumonia and non-bacteremic A-CAP. Moreover, in our region, serotype 1 was previously reported as

**Fig. 2.** Monthly rates (per 1000 children) of hospital visits for A-CAP in children <12, 12–23 and 24–59 months old, 2002 through 2013. Numbers represent declines in annual rates (calculated as IRR and 95% CI) compared to pre-PCV period. IRRs were adjusted for ethnic group and hospitalization.

**Fig. 3.** Yearly outpatients PER visits and hospitalization rates for A-CAP in children <5 years, in pre PCV, PCV7 and PCV13 periods. The numbers represent IRRs and 95% CI. IRR was adjusted for ethnicity and age, when appropriate. * For July 2002–June 2008, values are mean annual incidences; vertical lines represent 95% CI.
a common cause of bacteremic pneumonia in children <5 years [34]. Thus, the more pronounced impact of PCV13 on A-CAP rates compared with PCV7, may be associated with this serotype distribution. It is also possible that part of the further reduction in pneumonia observed during the PCV13 period is in fact due to a more prolonged period post-PCV introduction, since for the common PCV7/PCV13 serotypes, the start of the PCV era is July 2009.

Recently, Bonten et al. reported a significant efficacy of PCV13 against vaccine-serotype in CAP among elderly ≥65 years of age [35]. However, comparison between the efficacy (with no data so far on impact) of PCV13 in the elderly and post-vaccination impact in children seems inappropriate.

The widespread use of PCV13 is expected to have a marked impact on nasopharyngeal carriage of PCV13 serotypes, thus reducing their circulation, resulting in increased impact on pneumonia caused by these serotypes and extending protection to non-immunized populations [36,37].

In our study a linear and significant decline was observed in outpatient A-CAP episodes. However, after the introduction of PCV7, no reduction in hospitalization rates due to A-CAP was observed in all age groups and it is only after the introduction of PCV13 that a significant reduction in hospitalization rates was observed. These results are similar, at least to some extent, to previous studies reporting reduction in outpatient CAP cases in infants <2 years of age but not in other age groups after the introduction of the PCV7 into the US NIP [20]. This difference might be related to different distributions of the PCV13 serotypes between ages. This speculation is also consistent with the continuation of the trends after PCV13 introduction.

The non-reduction in hospitalization rates following PCV7 introduction observed in our study is in contrast to the ~40% reduction in all-cause pneumonia hospitalizations observed in the US among children <2 years, the age group most affected by the vaccine, both shortly after and 10 years after PCV7 introduction to the US NIP [4,18]. These differences may be related to a higher proportion of the additional PCV13 serotypes in our region compared to the US, mainly of serotypes 1 and 5.

It is possible that the increased proportion of hospitalized patients vs. outpatients observed in our study is related to other pathogens involved in CAP such as respiratory viruses, mainly RSV. In a previous study, we demonstrated that RSV plays an important role in A-CAP and this should be taken into account in order to determine direct vaccine efficacy mostly in the very young age group [38]. Thus, while PCVs reduced the rate of bacterial A-CAP, viral co-infection cases were not reduced. As these cases are associated with hypoxemia necessitating hospitalization, the rate of hospitalized A-CAP was not affected, especially in infants <1 year. Further studies should be conducted to support this observation.

Our study has several limitations. First, our results derive from only one region of our country. However, no changes in recommendations for the treatment and hospitalizations in this hospital were introduced during the study period. Moreover, results from previous studies and comparison of current data on IPD and bacteremic disease did not show that our region had any data suggesting it was different from the rest of the country (data not shown). Moreover, the fact that there is a single hospital in the region prevents variability in hospitalization practices and enables demonstration of real population-based effectiveness. Second, a possible limitation lies in the study case definition, based only on chest radiograph without any other clinical or laboratory parameters. However, we used the WHO chest radiograph definition as it has been used in many studies evaluating various PCVs efficacy and effectiveness. Additionally, it was demonstrated that this definition has a good correlation among observers and can be used to compare results in a study with more than one investigator [39]. The chest radiograph process used in this study (pediatricians and pediatric radiologist) was similar to the one recommended by the WHO working group [10]. Third, the fact that in our region two different populations live side by side and have different socioeconomic status and disease rates could have resulted in a somewhat different vaccine impact. However, to avoid any bias, our results were controlled for ethnicity and showed similar impact. Future studies should be conducted in order to determine the PCVs impact in these two populations. Fourth, although this study reported pre-vaccine results covering a 6-year period, we only were able to report so far a 4- and 3-year period since the introduction of PCV7 and PCV13, respectively. Ongoing studies should enable us to determine in the future the results of a longer term follow-up.

Fifth, this study used a very strict definition based on chest radiogram. S. pneumoniae can cause various clinical presentations of pneumonia which can be different from this definition. Thus, the effects of the pneumococcal conjugated vaccines are probably substantial compared to what is reported in the article. This definition was chosen since alveolar pneumonia is considered more related to bacterial etiology mainly of S. pneumoniae. In addition, a previous study looking at the efficacy of the PCVs in children with CAP, used this definition and thus we were able to compare the efficacy with the effectiveness that is reported in the present study. Studies using various different CAP definitions were conducted and reported, such as usage of the ICD-10 code [40].

In conclusion, a significant but moderate decline in hospital A-CAP visits in children <5 years old was observed already after PCV7 introduction, with a substantial additional reduction shortly after PCV13 introduction. Among outpatients, a significant decline was already observed after PCV7 introduction, while in hospitalized children significant declines were seen only following PCV13 introduction.

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Contributors

David Greenberg made substantial contributions to concept and design, participated in acquisition of data, analysis and interpretation of data, drafted the manuscript and revised it critically for important intellectual content and has approved the manuscript as submitted. Noga Givon-Lavi contributed to the concept and design, made substantial contributions to the analysis and interpretation of data, revised the manuscript critically for important intellectual content and has approved the manuscript as submitted. Shalom Ben-Shimol contributed to the concept and design and the analysis and interpretation of data; revised the manuscript critically for important intellectual content and has approved the manuscript as submitted. Jacob Bar Ziv contributed to the concept and design, critically reviewed the entire radiological diagnosis process, revised and approved the manuscript as submitted. Ron Dagan made substantial contributions to concept and design, to the acquisition and the analysis and interpretation of data, drafted the manuscript and revised it critically for important intellectual content and has approved the manuscript as submitted.

Conflict of interest statement

Financial disclosure: Ron Dagan has received grants/research support from MSD and Pfizer. He is a scientific consultant to
Genocia, MeD, MSD, and Pfizer and receives speaker’s fee from GlaxoSmithKline and Pfizer. David Greenberg is a speaker for Abbvie, Astra Zeneca, GlaxoSmithKline, MSD and Pfizer; a scientific consultant for Abbvie, A.T. (Advance Inhalation Therapy), Astra Zeneca, Enox Biopharma, GlaxoSmithKline, MSD and Pfizer; he has received grants from MSD and Abbvie and is a shareholder of A.T. and Enox Biopharma. All other authors declare having no conflicts of interest.

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