

Significant decline in pneumonia admission rate after the introduction of routine 2+1 dose schedule heptavalent pneumococcal conjugate vaccine (PCV7) in children under 5 years of age in Kielce, Poland

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Abstract This study was performed to estimate the effect of heptavalent pneumococcal conjugate vaccine (PCV7) on the pneumonia admission rate in children younger than 5 years of age, after the introduction of routine 2+1 dose schedule immunization. We compared the pneumonia admission rate (number of cases per 1,000 population) 2 years before and 2 years after the introduction of PCV7 in 2006. Only children with radiologically confirmed pneumonia were analyzed. The vaccination rate in the analyzed periods was around 99%. In the period preceding the implementation of PCV7, the average pneumonia admission rate was 41.48/1,000 and 6.15/1,000 for 1-year-old and 2–4-year-old children, respectively. Statistical analysis showed a significant fall in this rate in two consecutive years after PCV7 implementation ($p < 0.0000001$ for 1-year-old and $p = 0.011$ for 2–4-year-old children, respectively). In the first year of vaccination, the admission number decreased in these two groups by about 65 and 23%, respectively. In the second year, only a few percent fall in the admission rate was noted. In children younger than 2 years of age, the age group

targeted for vaccination, pneumonia-related healthcare utilization declined substantially following PCV7 introduction. These results suggest that PCV7 may play an important role in reducing the burden of pneumonia in Poland.

Introduction

Acute respiratory infections (ARIs) are among the leading causes of childhood morbidity and mortality, especially in developing countries [1]. The World Health Organization (WHO) data clearly indicate that *Streptococcus pneumoniae* is the most frequent cause of deaths worldwide and is responsible for >1.6 million deaths annually of children under 5 years of age, with pneumonia being the major cause [2]. Before the introduction of heptavalent pneumococcal conjugate vaccine (PCV7), the incidence of pneumonia in children below 5 years of age in Europe and USA was, similar to in Poland, around 34–40/1,000 [3–5]. *S. pneumoniae* was considered to be responsible for 17–44% of pneumonia-related hospitalizations in children in this age group [6–8]. PCV7 was included in the vaccination calendar initially in the USA (2000), and then, gradually, in about 45 other countries. Clinical trials showed that PCV7 had originally led to a completely unexpected reduction in the frequency of pneumonia, dating back to children below 5 years of age, depending on the applied analysis protocol, of 23.4% (Northern California Kaiser Permanente; NCKP) [9] or 30.3% (NCKP; reanalysis) [10] and intent-to-treat appropriately of 17.7% [9] and 25.5% [10]. In the postlicensure

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surveillance, Grijalva et al. [11] demonstrated that, for the end of the year 2004 compared with the pre-vaccination era (1997–1999), in children up to 2 years of age, a 39% reduction in all-cause pneumonia admission rates and a 65% fall in pneumococcal pneumonia hospitalizations could be observed. Comparing similar periods, Zhou et al. [12] demonstrated in children below 2 years of age a 52% reduction in the hospitalization rate and a 41.1% reduction in the number of clinic visits caused by all-cause pneumonia and 57.6 and 46.9%, respectively, for pneumococcal pneumonia (all differences were statistically significant; $p < 0.001$). Adam and Fehnle [13], in a study in which the 3+1 schedule was being applied, demonstrated a 38.4% reduction in all-cause pneumonia in risk groups, as compared to 10.9% in children without risk factors. Durando et al. [14], in an examination carried out on a free-of-charge PCV7 immunization program in Liguria, used a similar scheme to that of the present study (2+1 dose schedule in children aged 3, 5, and 11–12 months) and demonstrated a 15.2% reduction in all-cause pneumonia versus a 70.5% reduction in pneumococcal pneumonia.

In Poland, PCV7 remains the only recommended chargeable vaccination. In October 2008, the vaccinations were implemented at no cost only for children from risk groups. The overall vaccine uptake in Poland in the first year of life exceeded 98% and is constantly increasing for pneumococcal vaccination; it amounted to 41,000, 154,000, and 225,000 doses in 2006, 2007, and 2008, respectively. Starting from the end of 2008 to the end of January 2010, children from risk groups received a total of 50,000 doses of PCV7 (on average, 2,260 doses monthly).

Kielce is, so far, the only city in Poland where PCV7 was implemented as a compulsory and free-of-charge vaccination for all children in the 2+1 dose schedule system. There is only one children's hospital in the city which was allowed to be considered in our quasi-experimental design, in which we attempted to assess the influence of mass pneumococcal vaccination on the radiologically confirmed pneumonia admission rate, comparing their number in children in the age groups 0–1 year and 2–4 years in 2004 and 2005 (before implementing vaccination) and in 2007 and 2008 (two years after implementing city-wide immunization). We introduced the 2+1 dose schedule, which is officially recommended for mass vaccination, is employed in different countries, including Norway, Denmark, Finland, Italy, Ireland, Iceland, Sweden, and the United Kingdom, and also has an indirect effect among the unvaccinated population (herd immunity). The 3+1 dose schedule is recommended in Poland for individual vaccination and in risk groups as giving more reliable protection against invasive pneumococcal disease (IPD). For logistic reasons,

we start PCV7 vaccination in the third or fourth month of life, which is somewhat later than that generally recommended. Nonetheless, according to some data [13, 15, 16], this delay may render a better immunological response.

We also decided to check whether mass vaccination give rise to the so-called herd immunity effect manifested by a fall of pneumonia incidents in adults.

Materials and methods

In the period 2004–2008, the number of residents of Kielce dropped from approximately 209,000 to approximately 206,000. Despite the consistent drop in population number, the annual birth rate was still growing from 1,675 in 2004 to 1,879 in 2008.

In March 2006, by virtue of decision of the Kielce Municipal Council, city-wide free PCV7 vaccination (Prevenar[®]) was commenced. It involved children born from 1st January 2006 with permanent place of residence in Kielce. A 2+1 immunization scheme was applied—the first dose at the third or fourth month of life, and the second at the fifth or sixth month of life, combined with routine mandatory vaccinations—DTP, Hib, IPV; the third booster dose was administered in the 12–14th month, after vaccination with MMR vaccine.

According to the Provincial Sanitary and Epidemiological Station in Kielce, the performance rate of the vaccination was approximately 99% in the period analyzed. These data were double-checked. In the same period, the vaccination uptake was similar to other vaccinations: hepatitis B 99.84%; DTP+IPV 99.03%; and MMR 99.21% in 2006; hepatitis B 99.90%; DTP + IPV 99.45%; MMR 99.3%; and Hib 99.34% in 2007.

Polyclinic Children's Hospital is the only children's hospital in Kielce, thus, almost all of the children living in the city requiring hospitalization are admitted to there.

To assess the effect of pneumococcal vaccination (PCV7) on the pneumonia-related hospitalization rate, data concerning the number of hospitalizations in 2007 (second year of vaccination) and 2008 (third year) were compared with data concerning pneumonia hospitalizations in 2004 and 2005, i.e., before the vaccination program. In order to ascertain that the reported decline in hospitalization rate was not due to incidental causes, we compared the rates for pneumonia and acute diarrhoea (ICD10 codes: A04, A08, and A09). The hospitalization rate in the analyzed period (2006–2008) demonstrated a rising trend in all of the analyzed codes. Significance of the trends was verified using the log-linear model with quasi-Poisson errors.

Diagnosis of pneumonia was made on the basis of history, physical examination, and routine investigations

Table 1 Size of the child population in selected age groups and the number of pneumonia cases before (2004 and 2005) and after (2007 and 2008) implementation of the vaccination program

| Age (years) | Year | | | | | | | |
|-------------|----------|----------|----------|----------|----------|----------|----------|----------|
| | 2004 | | 2005 | | 2007 | | 2008 | |
| | <i>N</i> |
| 0–1 | 3,279 | 154 | 3,279 | 117 | 3,534 | 53 | 3,774 | 51 |
| 2–4 | 4,937 | 34 | 4,882 | 26 | 4,858 | 23 | 4,939 | 19 |

N—number of living children; *n*—number of pneumonia cases

(blood count, C-reactive protein [CRP], and erythrocyte sedimentation rate [ESR]). To ensure maximum reliability of the analysis, only pneumonia cases confirmed radiologically by two independent radiologists were taken into consideration and all cases of pneumonia were reassessed. Nearly all cases were coded in ICD10 as J18 and only a very small number as J15. None were encrypted as J13.

Data concerning the general number of pneumonia cases in Kielce for all age groups were derived from the Świętokrzyski Provincial Branch of the National Health Fund in Kielce.

The incidence rates were presented as the number of cases per 1,000 population and were calculated on the basis of the data available at the National Centre for Statistics in Poland (GUS). Analysis of covariance (ANCOVA) as a case of the general linear model (GLM) with binomial and negative binomial error structure was used for modeling pneumonia incidence. *p*-values <0.05 were considered as statistically significant. All data were analyzed using R version 2.2.1 and its “base” and “MASS” packages [17].

Results

Table 1 encompasses the number of hospitalizations due to radiologically confirmed pneumonia in children aged 0–1 year and 2–4 years, as well as the size of the population of Kielce in the years 2004, 2005, 2007, and 2008. In 2004 and 2005, i.e., in the period without mass vaccination, the incidence rate in the first year of life was 46.96/1,000 and 35.68/1,000, respectively (mean: 41.32/1,000), and in children aged 2–4 years, it was 6.88/1,000 and 5.32/1,000, respectively (mean: 6.11/1,000). Figure 1 presents the number of hospitalized pneumonia cases per 1,000 children residing in Kielce in the form of an average of two years preceding vaccination (2004 and 2005) and two subsequent years (2007 and 2008) after implementation of the vaccination program.

The risk of pneumonia hospitalization in children in their first year of life and between their second and fourth

years was modeled by a binomial distribution. Analysis based on the model revealed that the reduction of incidence rate in subsequent years in both age groups, as observed in Fig. 1, varied but was statistically significant (for children in their first year of life $p < 0.0000001$, for children aged 2–4 years $p = 0.01$). As early as in the first year after the implementation of vaccination, the number of hospitalized pneumonia cases in children aged 0–1 year decreased by almost 65%, and in children aged 2–4 years, it decreased by 23%. In 2008, a subsequent, but lower, decrease in hospitalization rate in both groups was observed, as presented in Fig. 1. The decrease was 10% in the group aged 0–1 year and 18% in the group aged 2–4 years. During the same period (2006–2008), the frequency of the admission rate for acute diarrhea as the internal control group showed a growing tendency. The log-linear model with quasi-Poisson errors revealed the observed trends to be significant ($p = 0.0173$) for all ICDs and there were no differences between A04, A08, and A09 in the rates of growth because the interaction between year and kind of ICDs was not significant.

Analysis of pneumonia incidence in individuals over 4 years of life revealed a significant diversity. Table 2 presents

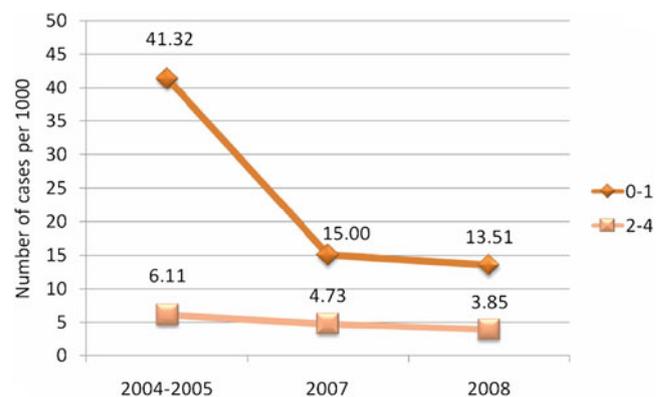


Fig. 1 Pneumonia hospitalization rates in age groups 0–1 and 2–4 years in Kielce before and after the introduction of pneumococcal vaccinations

Table 2 Size of the population of Kielce before (2004 and 2005) and after (2007 and 2008) implementation of the vaccination program in particular age groups and number of pneumonia cases

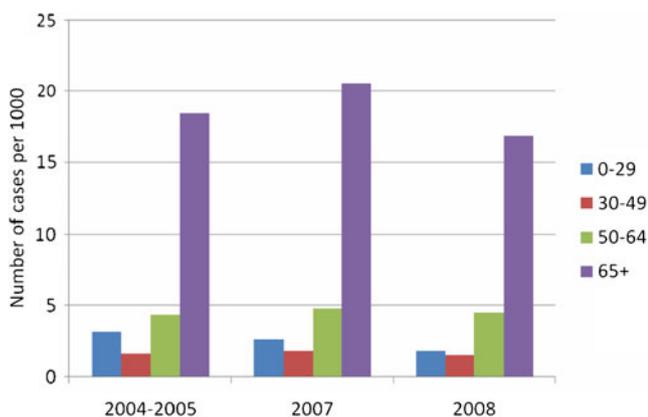
| Year | Age (years) | | | | | | | |
|------|-------------|----------|----------|----------|----------|----------|----------|----------|
| | 0–29 | | 30–49 | | 50–64 | | 65+ | |
| | <i>N</i> | <i>n</i> | <i>N</i> | <i>n</i> | <i>N</i> | <i>n</i> | <i>N</i> | <i>n</i> |
| 2004 | 81,479 | 282 | 58,787 | 110 | 42,247 | 178 | 26,942 | 469 |
| 2005 | 78,964 | 222 | 58,046 | 77 | 43,587 | 191 | 27,596 | 535 |
| 2007 | 74,210 | 192 | 57,351 | 103 | 45,989 | 217 | 28,357 | 581 |
| 2008 | 72,114 | 130 | 57,079 | 85 | 47,056 | 211 | 28,845 | 488 |

N—number of living individuals; *n*—number of pneumonia cases

the population size and number of pneumonia cases within four age groups in particular years. As is clearly visible, the highest incidence involved individuals aged above 65 years. Before the vaccination “era” in 2004, the incidence was 17.40/1,000 in this age group and 19.38/1,000 in 2005 (mean: 18.41/1,000). In 2007, the incidence in this age group was even higher, amounting to 20.48/1,000, but then it decreased to 16.91/1,000 in 2008.

Figure 2 presents the incidence rate per 1,000 residents in all of the age groups analyzed. The lowest incidence is observed in individuals aged between 30–49 years.

ANCOVA revealed that patient age is the only factor influencing the risk of disease. The positive slope of the variable indicates that the risk increases with age ($p=0.00133$). However, no evidence was found to prove that the implementation of mass vaccination resulted in a decrease of the incidence rate in individuals aged over 4 years ($p=0.5335$). The risk of pneumonia in non-vaccinated people in subsequent years remained unchanged in any age group. Interaction between the year of the study and patient age is not significant ($p=0.321$). It refers also to the age group 18–39 years, analyzed by Grijalva et al. [11], with the highest risk of contact with children. In our study, the incidence in this group was 0.71/1,000.

**Fig. 2** Incidence rate per 1,000 residents of Kielce in the various age groups analyzed

Discussion

We report that, after the introduction of a routine 2+1 dose schedule PCV7 immunization program in Kielce, Poland, admission rates for radiologically confirmed pneumonia decreased significantly for children younger than 5 years old who were the target population of the program. The reduction in the first year of life was 65% and between 2 and 4 years of age, it was 23%. This reduction in radiologically confirmed pneumonia provides an estimate of the vaccine-preventable burden of childhood pneumonia admissions attributable to *S. pneumoniae* in young children before PCV7 was introduced.

Randomized clinical trials showed that pneumococcal conjugate vaccines prevent pneumonia [9, 12, 13, 18, 19]. Efficacy estimates, however, varied according to the case definition of pneumonia. Vaccine efficacy against clinically diagnosed pneumonia was 6% for PCV7 in the NCKP trial [9] and 7% for a nine-valent PCV in the Gambian trial [18]. Vaccine efficacy estimates were consistently higher when radiological confirmation was included as part of the case definition—18% in the Kaiser Permanente trial [10], 17% in the South African trial [19], and 37% in the Gambian trial [18].

When the NCKP data were re-analyzed according to WHO radiological criteria for pneumonia diagnosis, the estimated vaccine efficacy was 26% [10]. The post-marketing study by Grijalva et al. [11] revealed a 39% decrease in the all-cause pneumonia admission rate among children up to 2 years of age and a 65% decrease in the rate of pneumonia defined as pneumococcal. Zhou et al. [12], comparing similar periods for children under 2 years of age, showed a 52% reduction of hospitalization and a 41.1% reduction of outpatient visits due to all-cause pneumonia and 57.6 and 46.9% for pneumococcal pneumonia, respectively.

Our findings are similar to the results of Grijalva et al. [11], Zhou et al. [12], and Durando et al. [14]. It can be that, in an open population, as in our study, the effect of a PCV7 immunization program is greater than that seen in clinical trials because herd immunity can have an important role in the reduction of disease in both vaccinated and

unvaccinated people, through decreases in the nasopharyngeal carriage of vaccine serotypes [20, 21].

Decline in the rates of all-cause pneumonia admissions in Kielce, Poland, suggests that *S. pneumoniae* was a major contributor to the burden of pneumonia admissions in young children in this town [22, 23], similar to in the USA, and provides an estimate of the burden of pneumococcal pneumonia admissions in young children due to PCV7 vaccine serotypes.

Unfortunately, in most cases in Poland, including in the city of Kielce, establishing the etiology of pneumonia is very difficult due to economic, logistic, and technical reasons. The research groups experienced these difficulties while conducting a sponsored epidemiological study [24] concerning the IPD frequency in Poland. In a 2-year period, only 134 samples fit for determining the etiological factor reached the central reference laboratory, of which as many as 108 were culture-negative.

Further, our study suggests a substantial effect on one of the most common reasons for hospital admissions not only in Kielce but throughout Poland and in other countries [21, 25, 26].

Observations similar to those for *S. pneumoniae* were made for *Haemophilus influenzae* type B pneumonia in Gambia, where substantial reductions in overall pneumonia were attributable to immunization with conjugate vaccines against this bacterium [27].

As evidenced in this study, surprisingly favorable results of PCV7 immunization may also be related to the relatively high serotype coverage of PCV7 vaccine in the Polish population, which, according to our findings, amounted to 73–77% in children under 5 years of age [24].

The 3+1 scheme of PCV7 vaccination is generally recognized and applied in many countries. However, the Municipal Council in Kielce decided to apply the 2+1 scheme, as it was not only cheaper, which was a particularly important factor in this case, but also, as evidenced in numerous studies [13, 15, 16, 28], was as efficient in a mass vaccination pattern as the original 3+1 scheme. The scheme was, thus, approved for population vaccination also in the registration dossier. Also in Poland, the 2+1 scheme proved to be efficient in population vaccination.

Previous findings showed that the group aged between 18 and 39 years had the second highest percentage decline in invasive pneumococcal disease after children younger than 5 years of age, suggesting a vaccine herd effect [20]. This age group includes parents of young children, so they could have benefited from reduced exposure to pneumococci when their children were immunized with PCV7.

The lack of an apparent decrease in pneumonia incidence in individuals after the fourth year of life, i.e., the so-called population effect, may be related to too a short period of vaccination and our observation, as well as to imperfect

coding and classification of pneumonia in adults, in particular, in outpatient settings.

The increase in birth rate, observed despite a systematic decrease in the city population size, may be explained by the willingness of young mothers to take advantage of free vaccination of their children, and, thus, their registration for permanent residence in Kielce.

This exceptionally high vaccination rate (99% vs., for instance, 93.4% reached in the best year in the Liguria Region program [14]) resulted not only from the good performance and efficacy of vaccination points, but most likely also from free-of-charge access to the vaccine. The cost of complete PCV7 vaccination, even in the 2+1 scheme, under the conditions of a private healthcare system, amounts to at least 25% of the average monthly salary in Poland.

Our study provides a comprehensive assessment of the changes in pneumonia admission rates after implementation of the PCV7 immunization program in Kielce, Poland. We used a strong quasi-experimental design to assess the effect of PCV7 vaccination. The observed reductions in radiologically confirmed pneumonia admissions suggest that, before the introduction of PCV7, *S. pneumoniae* was a major contributor to childhood pneumonia in Kielce, Poland, and provide an estimate of the burden of pneumococcal pneumonia admissions in young children due to PCV7 vaccine serotypes. Our results support the constantly growing evidence of the beneficial effects of the pneumococcal conjugate vaccines in children. Further, this substantial effect obtained in this study targeted one of the most common reasons for hospital admissions in Poland.

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