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# Effectiveness of a 2+1 dose schedule pneumococcal conjugate vaccination programme on invasive pneumococcal disease among children in Norway

Didrik F. Vestrheim*, Øistein Løvoll, Ingeborg S. Aaberge, Dominique A. Caugant, E. Arne Høiby, Hilde Bakke, Marianne R. Bergsaker

*Division of Infectious Disease Control, Norwegian Institute of Public Health, Norway*

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ABSTRACT

The 7-valent pneumococcal conjugate vaccine (PCV-7) was licensed in Norway in 2001. In July 2006, PCV-7 was introduced in the Norwegian Childhood Vaccination Programme in a 2+1 dose schedule, with immunizations administered at 3, 5 and 12 months of age. PCV-7 was offered through the vaccination programme to all children born from January 2006, i.e. a catch-up for children aged 3–6 months. Prior to 2006 the use of PCV-7 was negligible.

The effectiveness of the PCV-7 vaccination programme was assessed using data on invasive pneumococcal disease (IPD) incidence obtained from the Norwegian Surveillance System for Communicable Diseases, serotype distribution from the National Reference Laboratory for Pneumococci, and vaccine coverage and vaccination status from the Norwegian National Vaccination Register.

Vaccine coverage quickly reached high levels; 95% of children >3 months born from January 2006 had received at least one immunization with PCV-7. The incidence rate of IPD among children <2 years rapidly declined; the rate of vaccine serotype IPD in this age group fell from an average of 47.1 cases/100,000 population in the 2 years prior to PCV-7 introduction to 13.7 cases/100,000 population in 2007. The incidence rate of nonvaccine serotype IPD remained stable. The vaccine programme effectiveness was estimated to be 74% (95% CI 57–85%). No vaccine failure was seen after complete primary immunization with two vaccine doses. Our findings indicate that PCV-7 provides highly effective protection against vaccine serotype IPD when administered in a 2+1 dose schedule.



## 1. Introduction

A 7-valent conjugated pneumococcal vaccine (PCV-7) intended for use in children has been shown to be highly efficacious against invasive pneumococcal disease (IPD); a vaccine efficacy of 97.4% has been demonstrated when the vaccine is administered to infants in a four-dose regimen with three primary immunizations during the first year of life, and a booster in the second year of life [1]. PCV-7 was licensed in the United States in 2000, and a significant decline in IPD incidence rates among children under 2 years old was observed already in 2001 [2]. The decrease in IPD incidence rates extended beyond the target population to older children, adults and elderly persons [3,4]. Conjugate vaccines reduce nasopharyngeal carriage of *Streptococcus pneumoniae* belonging to the vaccine serotypes, i.e. serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, leading to a reduced transmission and, subsequently, to herd immunity [5]. At least twice as many cases of IPD are prevented indirectly by herd immunity as by the direct effect of vaccination [4].

Ninety-one serotypes of pneumococci are currently known [6,7]. PCV-7 covers the serotypes most commonly associated with IPD in children, although the serotype distribution, and thus the proportion of vaccine preventable IPD varies with time and geography [8,9]. During the 1990s the incidence rate of IPD increased in Norway, as in other Scandinavian countries [10,11]. In the period 1995–2001 the incidence rate of IPD was stable at approximately 19–20 cases/100,000 population, and vaccine serotype pneumococci were responsible for 73% of IPD in children <5 years [10]. However, the incidence rate of IPD caused by macrolide-resistant serotype 14 pneumococci in Norway started to increase in 2002, representing about 30% of cases in children aged less than 10 years by 2005 [12].

PCV-7 was licensed for use in a four-dose regimen, with three primary immunizations and a booster (3+1 schedule). However, the initial effects of vaccination in the United States were observed although complete immunization nationwide could not be per-

* Corresponding author at: Division of Infectious Disease Control, Department of Bacteriology and Immunology, Norwegian Institute of Public Health, PO Box 4404, Nydalen, NO-0403 Oslo, Norway. Tel.: +47 21 07 64 65; fax: +47 21 07 65 18.
*E-mail address:* didrik.frimann.vestrheim@fhi.no (D.F. Vestrheim).

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formed due to vaccine shortages. The effectiveness of three- and four-dose schedules seems to be similar in a case-control study [13], and comparable serological responses have been observed in children receiving either three or four vaccine doses [14]. However, experiences with a three-dose (2+1) schedule vaccination programme are lacking.

Through the Norwegian Childhood Vaccination Programme, immunizations are offered free of charge to all children living in Norway. PCV-7 was introduced in the Norwegian Childhood Vaccination Programme in July 2006, with catch up for all children born in 2006 [15]. Immunization followed a 2+1 dose schedule, with two primary immunizations at 3 and 5 months of age, and a booster at 12 months of age. In the Childhood Vaccination Programme, PCV-7 is administered concomitantly to established vaccination against diphtheria, tetanus, pertussis, polio and *Haemophilus influenzae* serotype b (DTP-IPV-Hib). This is the first report on the effectiveness of a 2+1 dose schedule of PCV-7 in a vaccination programme.

## 2. Materials and methods

### 2.1. Study population

The total Norwegian population aged <5 years in 2002–2007 was included in this study. PCV-7 was licensed in Norway in 2001. All vaccine doses are distributed by the Norwegian Institute of Public Health (NIPH). Prior to 2006 approximately 800 vaccine doses were distributed from NIPH, and in 2006, approximately 12,000 doses were distributed outside the vaccination programme. PCV-7 was introduced as a programme vaccine on 1 July 2006, and immunization has been offered to all children born in 2006 and onwards, i.e. a catch-up for children aged 3–6 months. Approximately 250,000 vaccine doses were administered through the vaccination programme in 2006 and 2007.

### 2.2. Surveillance of IPD

Cases of IPD were identified by the Norwegian Surveillance System for Communicable Diseases (MSIS) at the NIPH. IPD was defined as the identification of *S. pneumoniae* from a normally sterile body site, including positive culture from blood or cerebrospinal fluid (CSF), or detection of *S. pneumoniae* in CSF by antigen-tests or nucleic acid amplification. Surveillance of IPD has been ongoing since 1977, with mandatory notification of laboratory-confirmed cases of IPD by both the microbiology laboratory and the clinician, including data on clinical manifestations and previous vaccination.

*S. pneumoniae* isolates from cases of IPD were forwarded to the National Reference Laboratory for Pneumococci at NIPH and serotyped by the Quellung reaction using serotype-specific antisera (Statens Seruminstitut, Copenhagen, Denmark). Serotypes included in PCV-7, i.e. serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, were designated as vaccine serotypes, and all other serotypes were designated as nonvaccine serotypes. Antimicrobial susceptibility was screened by the disc diffusion test on Mueller-Hinton agar with 5% horse blood (before 18.12.2006: Neo-Sensitabs, Rosco Diagnostics, Taastrup, Denmark, after 18.12.2006: BD BBL Sensi-Discs, Becton, Dickinson and Company, Maryland, USA). For isolates with reduced susceptibility to one or more antimicrobial, minimum inhibitory concentrations (MICs) were determined using the Etest method (AB Biodisk, Solna, Sweden).

Following the introduction of PCV-7, MSIS requested local laboratories to forward missing isolates to the National Reference Laboratory for Pneumococci in order to get complete data on serotype distribution.

### 2.3. Surveillance of PCV-7 vaccine coverage

Immunizations administered through the Norwegian Childhood Vaccination Programme are mandatorily registered in the Norwegian National Vaccination Register (SYSVAK), and vaccine coverage in the study population was obtained from this register.

### 2.4. Surveillance of PCV-7 vaccine failure

A vaccine failure was defined as a case of IPD caused by a vaccine serotype with onset more than 2 weeks after complete primary immunization with two vaccine doses, but before booster immunization in a child younger than 13 months, or with onset more than 1 week after booster immunization in a child aged at least 12 months and having received a complete primary immunization before 12 months of age. For all cases of IPD among children a questionnaire regarding vaccination status and risk factors for infection was filled by the clinician. For possible cases of vaccine failure, the vaccination status of the patient was obtained by the questionnaire and confirmed by means of SYSVAK data.

### 2.5. Statistical analyses

IPD incidence rates were calculated using data from MSIS and population data from Statistics Norway, using yearly numbers as of 1 January. Age-specific IPD incidence rates were calculated for the age groups <1, 1, <2 and 2–4 years. A baseline incidence rate of IPD was calculated as an average of 2004 and 2005, the two last years before introduction of PCV-7. Serotype-specific IPD incidence rates were calculated for the age groups <1, 1, <2 and 2–4 years using the data available from the isolates forwarded to NIPH.

Changes in IPD incidence rates were calculated as incidence rate ratios (IRRs) with 95% confidence intervals (CIs) and $p$-values, using Episheet. Vaccine programme effectiveness was calculated as: $(1 - \text{IRR})100\%$. Two-sided $p$-values <0.05 were considered statistically significant. In order to account for missing isolates, we also calculated a vaccine programme effectiveness using IPD incidence rates estimated by assuming the same serotype distribution as for available isolates, and multiplying the overall incidence rate of IPD by the proportion of serotype-specific disease.

## 3. Results

### 3.1. Study population data

In the period from 2002 through 2007, the average population of Norway was 4,596,915. The average birth cohort was 56,953 children per year. During the study period, 523 cases of IPD among children aged <5 years were notified to MSIS.

### 3.2. PCV-7 vaccine coverage data

PCV-7 was offered to all children born after 1 January 2006, and by 1 January 2008, data on vaccine coverage showed that approximately 95% of children aged >3 months had received at least one immunization, approximately 90% of children aged >6 months had received two immunizations, and approximately 80% of children aged >13 months had received three immunizations.

### 3.3. Incidence rate of notified IPD

Prior to PCV-7 introduction, the incidence rate of IPD among children <5 years gradually increased, from 25.0 cases/100,000 population in 2002 to 42.9 cases/100,000 population in 2005, IRR

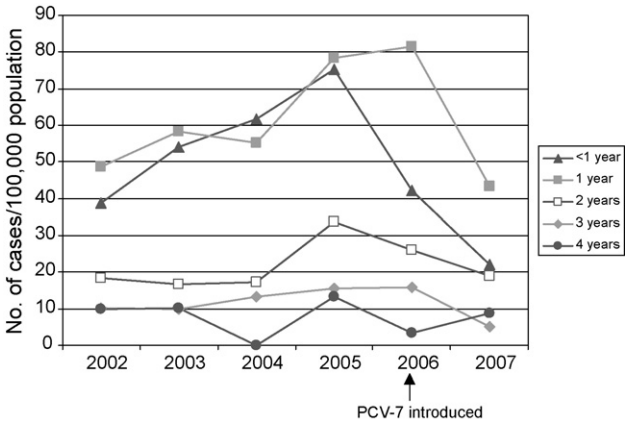


**Fig. 1.** Incidence rates (no. of cases/100,000 population) of invasive pneumococcal disease among children <5 years in Norway 2002–2007 by age and year of notification. The 7-valent pneumococcal conjugated vaccine was introduced in July 2006 and offered to all children born after 1 January 2006.

1.72 (95% CI 1.29–2.29), the increase being most pronounced among children aged <3 years as shown in Fig. 1.

The incidence rate of IPD among children aged <2 years decreased sharply from an average of 67.7 cases/100,000 population in the two pre-vaccine years to 32.6 cases/100,000 population in 2007, IRR 0.48 (95% CI 0.34–0.69). Age-specific incidence rates of IPD are shown in Fig. 1. A decline in the IPD incidence rate for children aged <1 year started in 2006 and continued in 2007, followed by a decline among 1-year olds starting in 2007. Age-specific incidence rates and IRRs showing the change from 2004–2005 to 2007 are listed in Table 1.

### 3.4. Incidence rate of serotype-specific IPD

A total of 454 isolates of *S. pneumoniae* from IPD in children aged <5 years were received at NIPH from 2002 to 2007. Following an intensified surveillance as of July 2006, the proportion of isolates forwarded to NIPH improved; direct communication with the diagnostic laboratories revealed that the remaining missing isolates either failed to be subcultured, or that the diagnose was reached by methods other than culture. The yearly proportions of isolates forwarded of the total number of notified cases are shown in Table 2. All isolates were serotyped. The yearly serotype distributions for the period 2002–2007 are shown in Table 2. With one exception, all isolates were recovered from either blood or CSF; the proportion of isolates recovered from CSF each year ranged from 7.3% to 22.9%. One isolate, serotype 3, was recovered from synovial fluid.

During the 4 years prior to introduction of PCV-7 in the vaccination programme, an increased incidence rate of vaccine serotype IPD was observed among children <5 years, from 13.5 cases/100,000 in 2002 to 28.0 cases/100,000 in 2005, IRR 2.08 (95% CI 1.42–3.03). The most prevalent vaccine serotype, serotype 14, was a major contributor to the pre-PCV-7 increase among children; the incidence rate of IPD caused by serotype 14 pneumococci increased from 3.71 cases/100,000 in 2002 to 12.5 cases/100,000 in 2005, IRR 3.35 (95% CI 1.71–6.59).

After introduction of PCV-7, an overall decline of vaccine serotype IPD was observed among children aged <5 years when compared to the pre-PCV-7 baseline (Table 1). Statistically significant reductions in vaccine serotype IPD were observed among children aged <1 year (IRR 0.08, 95% CI 0.02–0.35), and for 1-year olds (IRR 0.45, 95% CI 0.25–0.81) (Table 1).

### 3.5. Antimicrobial susceptibility

Throughout the surveillance period, 11 penicillin non-susceptible pneumococcal isolates were identified, ranging from 0 to 4 isolates per year. The incidence rate of IPD caused by macrolide-resistant pneumococci among children <5 years increased from 3.03 cases/100,000 population in 2003 to 11.75 cases/100,000 population in 2005, IRR 3.87 (95% CI 1.86–8.07).

**Table 1**
Invasive pneumococcal disease incidence rates among children <5 years in Norway before (2004–2005) and after (2007) introduction of the 7-valent pneumococcal conjugated vaccine (PCV-7)

| Age | Total no. of cases[a] | | No. of cases/100,000 population | | Incidence rate ratio (95% CI)[b] | *p*-Value[c] |
|---|---|---|---|---|---|---|
| | 2004–2005 | 2007 | 2004–2005 | 2007 | | |
| Notified cases of IPD[d] | | | | | | |
| <1 year | 39 | 13 | 68.6 | 22.1 | 0.32 (0.18–0.58) | <0.01 |
| 1 year | 38 | 25 | 66.9 | 43.3 | 0.65 (0.41–1.02) | 0.06 |
| 2–4 years | 27 | 19 | 23.6 | 11.0 | 0.46 (0.28–0.78) | <0.01 |
| <5 years overall | 104 | 57 | 36.0 | 19.7 | 0.55 (0.41–0.73) | <0.01 |
| Vaccine serotype IPD[e,f] | | | | | | |
| <1 year | 23 | 2 | 40.5 | 3.4 | 0.08 (0.02–0.35) | <0.01 |
| 1 year | 30.5 | 14 | 53.7 | 24.3 | 0.45 (0.25–0.81) | <0.01 |
| 2–4 years | 15.5 | 13 | 13.5 | 7.5 | 0.55 (0.29–1.06) | 0.07 |
| <5 years overall | 69 | 29 | 23.9 | 10.0 | 0.42 (0.28–0.63) | <0.01 |
| Nonvaccine serotype IPD[g,f] | | | | | | |
| <1 year | 9 | 10 | 15.8 | 17.0 | 1.08 (0.50–2.33) | 0.85 |
| 1 year | 5.5 | 10 | 9.7 | 17.3 | 1.79 (0.76–4.22) | 0.18 |
| 2–4 years | 8.5 | 6 | 7.4 | 3.5 | 0.47 (0.18–1.18) | 0.10 |
| <5 years overall | 23 | 26 | 8.0 | 9.0 | 1.10 (0.70–1.82) | 0.63 |
| Macrolide-resistant IPD[h,f] | | | | | | |
| <5 years overall | 25.5 | 8 | 8.8 | 2.8 | 0.31 (0.15–0.66) | <0.01 |

[a] No. of cases and incidence rates for 2004–2005 are given as the average for the 2 years.
[b] Incidence rate ratios and 95% confidence intervals (CI) were calculated using Episheet.
[c] *p*-Values were calculated using Episheet.
[d] IPD; invasive pneumococcal disease.
[e] Vaccine serotype; the serotypes included in 7-valent conjugated pneumococcal vaccine, i.e. serotypes 4, 6B, 9V, 14, 18C, 19F, 23F.
[f] No. of cases and incidence rates were calculated using available isolates.
[g] Nonvaccine serotype; serotypes not included in the 7-valent conjugated pneumococcal vaccine.
[h] Macrolide-resistant IPD: IPD caused by pneumococci resistant to erythromycin and/or clindamycin.

**Table 2**
Yearly serotype distribution of *Streptococcus pneumoniae* from cases of invasive pneumococcal disease among children aged <5 years in Norway, 2002–2007

| | No. of isolates | | | | | |
|---|---|---|---|---|---|---|
| | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 |
| Vaccine serotypes[a] | | | | | | |
| 4 | – | 2 | 3 | 6 | 10 | 1 |
| 6B | 13 | 10 | 12 | 19 | 6 | 6 |
| 9V | 2 | 5 | 3 | 3 | 8 | 2 |
| 14 | 11 | 17 | 29 | 36 | 27 | 11 |
| 18C | 7 | 7 | 1 | 8 | 7 | 4 |
| 19F | 2 | 2 | 5 | 3 | 2 | 3 |
| 23F | 5 | 3 | 4 | 6 | 7 | 2 |
| Total | 40 | 46 | 57 | 81 | 64 | 29 |
| Nonvaccine serotypes[b,c] | | | | | | |
| 1 | 3 | 10 | 5 | 6 | 2 | 2 |
| 3 | – | 3 | 1 | 4 | 2 | 3 |
| 6A | 1 | – | 5 | 2 | 6 | 3 |
| 7F | 3 | 6 | 5 | 5 | 4 | 5 |
| 33F | – | 1 | – | – | 1 | 4 |
| Total | 16 | 24 | 23 | 23 | 23 | 25 |
| Total | 56 | 70 | 80 | 104 | 90 | 54 |
| Macrolide-resistant isolates[d] | 9 | 7 | 19 | 34 | 19 | 8 |
| Proportion available isolates (%)[e] | 75.7 | 80.5 | 95.2 | 83.9 | 92.8 | 96.5 |

PCV-7 was introduced in the Norwegian Childhood Vaccination Programme 1 July 2006 and offered to all children born after 1 January 2006.

[a] Vaccine serotype; the serotypes included in 7-valent conjugated pneumococcal vaccine, i.e. serotypes 4, 6B, 9V, 14, 18C, 19F, 23F.

[b] Nonvaccine serotype; serotypes not included in the 7-valent conjugated pneumococcal vaccine.

[c] Only serotypes with more than two isolates per year are shown in the table.

[d] Macrolide-resistant isolates: pneumococcal isolates resistant to erythromycin and/or clindamycin.

[e] Proportion of notified cases for which a corresponding pneumococcal isolate was available at the reference laboratory.

After introduction of PCV-7, the incidence rate declined to 2.8 cases/100,000 population in 2007, IRR 0.31 (95% CI 0.15–0.66) when compared to the pre-PCV-baseline (Table 1). Serotype 14 pneumococci constituted nearly 90% of the macrolide-resistant isolates in this period.

### 3.6. Vaccine failure

Among children born from January 2006 for which data on serotype was available, no vaccine failure was observed. Two cases of invasive disease occurred in partially vaccinated children; an 8-month-old with IPD 8 weeks after the first dose (serotype 6B), and a 4-month-old with IPD 6 weeks after the first dose (serotype 18C).

### 3.7. Vaccine programme effectiveness

Among children <2 years of age, a vaccine programme effectiveness of 71% (95% CI 51–83%) was demonstrated by the decline of vaccine serotype IPD. When accounting for missing isolates, the vaccine programme effectiveness was estimated to be 74% (95% CI 57–85%). No significant increase in nonvaccine serotype IPD was observed after introduction of PCV-7.

## 4. Discussion

The vaccine coverage for PCV-7 reached high levels soon after introduction in the Norwegian Childhood Vaccination Programme in July 2006. The incidence rate of IPD rapidly declined in the population targeted for vaccination; a significant decrease among children <1 year was observed already in 2006. This decrease continued in 2007, when a decrease among 1-year olds was also achieved. Thus, the initial decline in IPD incidence rates follows the 2006 birth cohort, the first cohort offered PCV-7. In this report we have estimated the effectiveness of the vaccine programme to be 74% among children aged <2 years, 18 months after implementation of PCV-7. A decline in IPD incidence rates were also noted among 2-year olds and 3-year olds, which might be due to a starting herd effect. However, the total number of IPD cases among the 2- and 3-year olds is small, and the overall decline is influenced by a concomitant decrease in nonvaccine serotype IPD.

The use of PCV-7 in Norway prior to 2006 was limited; as few as approximately 800 doses were distributed from 2001 to 2006. When implementing PCV-7 in the Norwegian Childhood Vaccination Programme, a catch-up was offered to children born in 2006, i.e., children aged 3–6 months. However, in the first half of 2006, approximately 12,000 doses of PCV-7 were distributed outside the vaccination programme, possibly due to an increased awareness of vaccine availability. Hence, an increased use of PCV-7 in 2006 among children aged >6 months in 2006 might influence the small decline in IPD among 2- and 3-year olds observed in 2007.

No vaccine failure was identified among children who had received at least two immunizations with PCV-7 through the Norwegian Childhood Vaccination Programme. This clearly indicates a very high efficacy of two primary immunizations with PCV-7. A case-control study is planned in order to investigate vaccine effectiveness further.

During the 4 years prior to introduction of PCV-7 in the Norwegian Childhood Vaccination Programme, the incidence rate of IPD among children aged <2 years increased significantly, due to an increase of vaccine serotype IPD. The rapid spread of a macrolide-resistant serotype 14 clone, the England$^{14}$-9 clone in Norway has previously been described [12]. The incidence rate of IPD caused by this clone started to increase in 2002, and by 2005 it accounted for 30% of IPD cases among children <10 years of age. Thus, the pre-PCV-7 increase in vaccine serotype IPD incidence rate was to a large extent driven by clonal expansion of macrolide-resistant serotype 14 pneumococci. No changes in diagnostic practices or methods have been implemented recently, and the pre-PCV-7 changes are believed to represent a true epidemiological trend rather than altered diagnostic sensitivity or blood culturing practice. Following the introduction of PCV-7, the incidence rate of IPD caused by macrolide-resistant pneumococci significantly declined. Hence, the conjugate vaccine has effectively limited the spread of these resistant pneumococci in the community, as has also been demonstrated in the United States after licensure of PCV-7 [16]. The incidence rate of IPD caused by penicillin non-susceptible pneumococci was low and unchanged throughout the study period.

In this report, we have calculated changes using average baseline disease incidence rates of 2004–2005. Due to the pre-PCV-7 increase in IPD incidence rate from 2004 to 2005, this might falsely result in an underestimate of the post-PCV-7 changes, compared to the changes from 2005 to 2007. In the United States, a 78% (95% CI 74–82%) decline in vaccine serotype IPD among children <2 years was observed in 2001, 1 year after licensure of PCV-7 [2]. This effect was somewhat higher than the estimated vaccine programme effectiveness of 74% (95% CI 57–85%) among children <2 years observed in our study. However, the baseline incidence rate of IPD among children aged <2 years in Norway was lower than in the United States prior to PCV-7 introduction; 67.7 cases/100,000 population and 188.0 cases/100,000 population, respectively. Similarly, the estimated serotype coverage of PCV-7 was lower in Norway than in the United States; 78.5% and 83.1%, respectively. Thus, the incidence rate of vaccine serotype IPD, i.e. IPD preventable by PCV-7, and the potential for reductions in vaccine serotype IPD incidence rates at the onset of vaccination was higher in the United

States compared to Norway. In the United States, blood cultures are obtained both in outpatient clinics and in hospitals, while in Norway, this procedure is only carried out in hospitals. More frequent blood culturing in the United States, yielding more positive samples, might in part explain the higher rate of IPD in the United States as compared to Norway.

Conjugated vaccines reduce nasopharyngeal carriage of vaccine serotype pneumococci, leading to reduced transmission and, subsequently, to herd immunity [5]. At least twice as many cases of IPD are prevented indirectly by herd immunity as by the direct effect of vaccination [4]. Reduced carriage of vaccine serotype pneumococci in 1-year olds has been demonstrated after only one immunization with a conjugated vaccine [17]. Based on experiences during the first years after licensure of PCV-7 in the United States it has been modelled that vaccination with even less than three doses, and incomplete vaccination coverage, may be able to induce herd immunity [18]. The magnitude of the indirect effect of PCV-7 in Norway following a 2+1 dose schedule with high vaccine coverage remains to be evaluated.

By reduced carriage of vaccine serotype in the population following the introduction of PCV-7, an ecological niche is created in the nasopharynx, in which vaccine serotypes might be replaced by nonvaccine serotypes, a phenomenon called serotype replacement [19]. The increased prevalence of carriage of nonvaccine serotypes might lead to an increased incidence rate of nonvaccine serotype IPD in the population. Several reports describe such serotype replacement IPD in the United States after the licensure of PCV-7 in 2000 [20,21]. Replacement IPD seems to be more prominent in the older age-groups than among children [21]. No significant increase in nonvaccine serotype IPD was found among children in Norway, although a small increase of serotype 33F IPD was noted (from no cases in 2004–2005 to four cases in 2007). However, serotype replacement might increase and be more evident with time.

By the use of reduced dose vaccination schedules, the cost of vaccination can be substantially reduced. This has great implications for introduction of PCV-7 in national immunization programmes, especially for low income countries. The 2+1 dose schedule further has the advantage of being compatible with many national immunization programmes, including those of many developing countries [22]. However, the total cost-effectiveness of the vaccination programme is influenced by the herd immunity induced. A Norwegian study of cost-effectiveness of a PCV-7 vaccination programme concluded that a three dose schedule would be cost saving, when assuming the same effect of three vaccine doses as four doses, and accounting for herd immunity and indirect costs [23]. The experience from Norway so far, with no registered vaccine failure, indicates that the direct effect of a three-dose vaccination schedule in is comparable to that of a four-dose schedule.

This report on the direct effect of vaccination indicates that PCV-7 administered in a 2+1 dose schedule is highly effective against vaccine-preventable IPD, as demonstrated by an early, estimated vaccine programme effectiveness of 74% among children aged <2 years. Importantly, no vaccine failure was observed. Further follow-up is needed in order to obtain more definite results, and to establish the impact of the 2+1 dose schedule on herd immunity.

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## References

[1] Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. Pediatr Infect Dis J 2000;19:189–95.
[2] Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med 2003;348:1737–46.
[3] Lexau CA, Lynfield R, Danila R, Pilishvili T, Facklam R, Farley MM, et al. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. JAMA 2005;294:2043–51.
[4] Centers for Disease Control and Prevention. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease—United States, 1998–2003. MMWR Morb Mortal Wkly Rep 2005;54:893–7.
[5] O'Brien KL, Millar EV, Zell ER, Bronsdon M, Weatherholtz R, Reid R, et al. Effect of pneumococcal conjugate vaccine on nasopharyngeal colonization among immunized and unimmunized children in a community-randomized trial. J Infect Dis 2007;196:1211–20.
[6] Henrichsen J. Six newly recognized types of *Streptococcus pneumoniae*. J Clin Microbiol 1995;33:2759–62.
[7] Park IH, Pritchard DG, Cartee R, Brandao A, Brandileone MC, Nahm MH. Discovery of a new capsular serotype (6C) within serogroup 6 of *Streptococcus pneumoniae*. J Clin Microbiol 2007;45:1225–33.
[8] Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. Clin Infect Dis 2000;30:100–21.
[9] Feikin DR, Klugman KP. Historical changes in pneumococcal serogroup distribution: implications for the era of pneumococcal conjugate vaccines. Clin Infect Dis 2002;35:547–55.
[10] Pedersen MK, Hoiby EA, Froholm LO, Hasseltvedt V, Lermark G, Caugant DA. Systemic pneumococcal disease in Norway 1995–2001: capsular serotypes and antimicrobial resistance. Epidemiol Infect 2004;132:167–75.
[11] Henriques NB, Kalin M, Ortqvist A, Akerlund T, Liljequist BO, Hedlund J, et al. Dynamics of penicillin-susceptible clones in invasive pneumococcal disease. J Infect Dis 2001;184:861–9.
[12] Sogstad MK, Littauer P, Aaberge IS, Caugant DA, Hoiby A. Rapid spread in Norway of an erythromycin-resistant pneumococcal clone, despite low usage of macrolides. Microb Drug Resist 2007;13:29–36.
[13] Whitney CG, Pilishvili T, Farley MM, Shaffner W, Craig AS, Lynfield R, et al. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet 2006;368:1495–502.
[14] Kayhty H, Ahman H, Eriksson K, Sorberg M, Nilsson L. Immunogenicity and tolerability of a heptavalent pneumococcal conjugate vaccine administered at 3, 5 and 12 months of age. Pediatr Infect Dis J 2005;24:108–14.
[15] Bergsaker MA, Feiring B. Introduction of pneumococcal conjugate vaccine into the Norwegian childhood vaccination programme. Eurosurveillance 2006;11:060202.
[16] Stephens DS, Zughaier SM, Whitney CG, Baughman WS, Barker L, Gay K, et al. Incidence of macrolide resistance in *Streptococcus pneumoniae* after introduction of the pneumococcal conjugate vaccine: population-based assessment. Lancet 2005;365:855–63.
[17] Dagan R, Melamed R, Muallem M, Piglansky L, Greenberg D, Abramson O, et al. Reduction of nasopharyngeal carriage of pneumococci during the second year of life by a heptavalent conjugate pneumococcal vaccine. J Infect Dis 1996;174:1271–8.
[18] Haber M, Barskey A, Baughman W, Barker L, Whitney CG, Shaw KM, et al. Herd immunity and pneumococcal conjugate vaccine: a quantitative model. Vaccine 2007;25:5390–8.
[19] Spratt BG, Greenwood BM. Prevention of pneumococcal disease by vaccination: does serotype replacement matter? Lancet 2000;356:1211.
[20] Kaplan SL, Mason Jr EO, Wald ER, Schutze GE, Bradley JS, Tan TQ, et al. Decrease of invasive pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine. Pediatrics 2004;113:443–9.
[21] Hicks LA, Harrison LH, Flannery B, Hadler JL, Schaffner W, Craig AS. Incidence of pneumococcal disease due to non-pneumococcal conjugate vaccine (PCV7) serotypes in the United States during the era of widespread PCV7 vaccination, 1998–2004. J Infect Dis 2007;196:1346–54.
[22] Pneumococcal conjugate vaccine for childhood immunization – WHO position paper. Wkly Epidemiol Rec 2007;82:93–104.
[23] Wisloff T, Abrahamsen TG, Bergsaker MA, Løvoll Ø, Møller P, Pedersen MK, et al. Cost effectiveness of adding 7-valent pneumococcal conjugate (PCV-7) vaccine to the Norwegian childhood vaccination program. Vaccine 2006;24:5690–9.