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Impact of pneumococcal vaccination in Denmark during the first 3 years after PCV introduction in the childhood immunization programme

Helene Ingels[a,*], Jeppe Rasmussen[b], Peter Henrik Andersen[b], Zitta B. Harboe[a], Steffen Glismann[b], Helle Konradsen[a], Steen Hoffmann[a], Palle Valentiner-Branth[b], Lotte Lambertsen[a], On behalf of Danish Pneumococcal Surveillance Collaboration Group 2009–2010[1]

[a] Neisseria and Streptococcus Reference Laboratory, Department of Microbiological Surveillance and Research, Statens Serum Institut (SSI), Copenhagen, Denmark
[b] Department of Epidemiology, SSI, Copenhagen, Denmark

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ABSTRACT

Background and aims: The 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in Denmark in October 2007 in a 2+1 schedule with a catch-up programme for children up to 17 months of age. To assess the impact of PCV we evaluated on the whole population: (1) direct and indirect effects on incidence of invasive pneumococcal disease (IPD), (2) changes in pneumococcal serotype distribution and (3) IPD related mortality.

Methods: We compared disease incidence in pre-PCV (years 2000–2007) and PCV periods (years 2008–2010) based on national surveillance data.

Results: In children aged 0–5 years the overall incidence of IPD decreased from 26.7 to 16.3 cases per 100,000 (IRR 0.58; 95% Confidence Interval (CI) [0.48–0.69]) and case fatality declined from 1.8% (12 deaths) in the eight-year pre-PCV period to 0% (no deaths) in the three-year PCV period. In the whole population the overall incidence of IPD and of IPD caused by vaccine serotypes declined significantly from 19.5 to 17.7 and from 7.7 to 3.8 cases per 100,000 persons comparing the two periods. The incidence of IPD due to non-vaccine serotypes (NVT-IPD) increased significantly from 11.8 to 13.9 cases per 100,000 in the whole population (incidence rate ratio 1.18; 95% CI [1.12–1.24]) with predominance of the serotypes 1.7F and 19A.

Conclusions: We report a marked decline in incidence in IPD in both vaccinated and non-vaccinated age groups and a minor but statistically significant increase in incidence of IPD due to NVTs in both vaccinated and non-vaccinated groups with predominance of serotypes covered by higher valence pneumococcal conjugate vaccines.

1. Introduction

Worldwide *Streptococcus pneumoniae* is a leading cause of severe bacterial infectious diseases. WHO has estimated that pneumococci cause 1.4 million child deaths annually [1].

The seven-valent pneumococcal conjugate vaccine (PCV7) was licensed in 2000 and is effective in preventing invasive pneumococcal disease (IPD) caused by the included serotypes [2,3] even with a reduced dose schedule of 2+1 doses [4–6] alternative to the 3+1 doses schedule recommended initially by the manufacturer [2]. Recently, conjugate vaccines with broadened serotype coverage have been licensed. Vaccination with conjugated vaccines reduces nasopharyngeal carriage of the pneumococcal serotypes covered by the vaccine, the vaccine serotypes (VTs). The reduced prevalence of carriage can lead to important reduction in pneumococcal disease caused by VTs in other age groups due to less transmission of VTs. This indirect vaccine effect has been reported from several countries since PCV implementation [7–9] and has had major health

Abbreviations: CI, confidence interval; IPD, invasive pneumococcal disease; NVT, non-vaccine serotype; NVT-IPD, non-vaccine serotype invasive pneumococcal disease; NVT-PM, non-vaccine serotype pneumococcal meningitis; PM, pneumococcal meningitis; PCV7, 7-valent pneumococcal conjugate vaccine; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; VT, vaccine serotype; VT-IPD, vaccine serotype invasive pneumococcal disease; VT-PM, vaccine serotype pneumococcal meningitis.

* Corresponding author at: National Neisseria and Streptococcus Reference Laboratory, Department of Microbiological Surveillance and Research, Statens Serum Institut, Artillerivej 5, DK 2300 Copenhagen, Denmark. Tel.: +45 32683622; fax: +45 32683873.
E-mail addresses: HIG@ssi.dk, helene_ingels@yahoo.dk (H. Ingels).

[1] See Appendix A.

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economic benefit. However, the PCV induced removal of VT pneumococci from nasopharynx opens a niche for non-vaccine serotype (NVT) pneumococci or other bacteria in general [10,11]. Replacement has also been observed in IPD following PCV introduction several countries following PCV introduction as well [5,9,12].

Use of PCVs has been successful in reducing VT-IPD in many countries worldwide, but large differences across nations have been observed in disease epidemiology after paediatric PCV implementation [7,9,12,13]. Various models have been developed to take account of as many factors as possible that influence the dynamics of pneumococcal epidemiology. In spite of this it has been difficult to predict the effects of PCV introduction in individual countries and to which extent the decrease in VT-IPD has been counteracted by an increase in NVT-IPD. Factors responsible for these differences may include: differences in implemented vaccination schedules, vaccination uptake, antibiotic usage and resistance, and the prevalence of PCV7 serotypes in the population prior to vaccination [9,13]. Other differences between countries influencing the observation of vaccine impact could be differences in surveillance systems as well as differences in care seeking and blood culturing practices [9,13]. Surveillance reports after vaccine implementation from individual countries are therefore of great value.

Since October 2007 PCV7 has been given in a 2 + 1 dose schedule in the Danish national immunization programme for infants with a catch-up programme for children up to 17 months of age. Shortly after the introduction of the PCV7 a high coverage and a high effectiveness of the vaccine programme against paediatric VT-IPD was reported [14]. Denmark is a country with low antibiotic consumption and with a laboratory based surveillance of IPD, including serotyping, which goes back to 1938 [15,16].

In this report, we assess the impact of paediatric PCV vaccination on the whole population in Denmark after the first three years of the vaccination programme by evaluating: (1) direct and indirect effects on incidence of IPD, (2) changes in pneumococcal serotype distribution and (3) changes in IPD related mortality.

2. Materials and methods

2.1. Study population

The study cohort comprises the population of Denmark in the years 2000–2010 with a population of approximately 5,500,000 inhabitants (varying from 5,330,020 to 5,534,738 in the study years) [17].

2.2. Definitions

Invasive pneumococcal disease (IPD). A case of IPD was defined as a positive culture of *S. pneumoniae* from cerebrospinal fluid (CSF), blood or any other normally sterile clinical sample sites. Only one isolate per patient was included unless clinical sample dates were more than 30 days apart or the serotypes of isolates were different. If both CSF and blood isolates were received for a case, the case was categorized as pneumococcal meningitis (PM).

Periods. Pre-PCV was defined as the time period 2000 to 2007 inclusive and PCV as the period 2008 to 2010 inclusive.

Vaccine type-IPD (VT-IPD) and vaccine type-PM (VT-PM). IPD or PM caused by one of the pneumococcal serotypes included in PCV7: 4, 6B, 9V, 14, 18C, 19F, and 23F.

Non-vaccine type-IPD (NVT-IPD) and non-vaccine type-PM (NVT-PM). IPD or PM caused by one of the pneumococcal serotypes not included in the PCV7. See details above.

PCV-failure. A case of vaccine failure was defined as a case of VT-IPD in a vaccinated child, with IPD onset more than two weeks after complete primary immunization with two vaccine doses.

Case fatality. Death was considered to be related to IPD, when the date of death was within 30-days after the clinical sample date from the patient. Vital status of patients was retrieved through the surveillance system as describe previously [14].

Estimation of prevented number of death. The number death prevented in the PCV period was estimated from the number of death related to IPD (as describe above) per year in the pre-PCV time period.

2.3. Pneumococcal vaccination in Denmark

The PCV7 vaccine was offered to all children free of charge as part of the childhood immunization programme since October 1, 2007 in a 2 + 1 schedule at the ages of 3, 5, and 12 months. During the introduction period a catch-up programme for children up to 17 months of age was carried out as previously described [14]. From April 19, 2010 the 13-valent pneumococcal conjugate vaccine (PCV13) was delivered in place of PCV7. Use of stocks of PCV7 was recommended before use of PCV13. Usage of PCV13 was therefore slowly commenced throughout 2010. Information about which PCV was given, was obtained from contact with physicians and based on this we define 2010 as a year predominated by PCV7.

Before PCV use in the childhood immunization programme pneumococcal vaccines were used at a very low level. PCV7 was recommended for use for certain paediatric risk groups age 0–2 since 2001 [18] and the 23-valent polysaccharide based vaccine has been licensed and in use for risk groups of children above 2 years and adults since the early 1980s [19].

2.4. National surveillance of IPD and vaccine coverage

The surveillance system has been described in detail elsewhere [14]. Briefly, all departments of clinical microbiology in Denmark submit invasive *S. pneumoniae* isolates for determination of serotype to the National Neisseria and Streptococcus Reference Laboratory (NSR). It has been estimated that more than 90% of all IPD isolates are submitted to the reference laboratory (NSR) [20]. Isolates are almost exclusively obtained from hospitalized patients.

Immunizations administered through the Danish Childhood Vaccination Programme are since 1990 registered in the Danish National Vaccination Registry. Vaccine uptake was calculated on the basis of person-identifiable data from this vaccination registry by using the administrative service codes indicated by general practitioners, when settling the first, second and third PCV dose of vaccine.

2.5. Microbiological testing

The bacterial isolates were confirmed as pneumococci and serotyped by use of Pneumotest latex and Quellung reaction using type-specific pneumococcal rabbit antisera as previously described [21,22]. Since 2007 cases of serotype 6C were distinguished from serotype 6A cases, but before 2007 6A includes both serotypes 6A and 6C.

2.6. Statistical analyses

IPD incidence rates were estimated based on surveillance data on IPD and population data from Statistics Denmark using yearly population numbers. Age-specific IPD incidences were determined and by using the pre-PCV period (2000–2007) as a baseline, changes in IPD incidence rates were calculated as incidence rate ratios (IRRs) with 95% confidence intervals (CIs). Two-sided p-values <0.05 were considered statistically significant.

Minor differences in the exact numbers of cases are to be found upon comparing data used in this study and the previous published