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Four years of universal pneumococcal conjugate infant vaccination in Germany: Impact on incidence of invasive pneumococcal disease and serotype distribution in children

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ABSTRACT

Introduction: Vaccination with pneumococcal conjugate vaccine (PCV) for all children <2 years was recommended in Germany in July 2006. Initially PCV7 was exclusively used; PCV10 became available from April 2009 and PCV7 was replaced by PCV13 in December 2009.
Objective: To compare the incidence and serotype distribution of invasive pneumococcal disease (IPD) for pneumococcal meningitis and non-meningitis IPD in children from 2007 to 2010 with reference to the pre-vaccination period from 1997 to 2001.
Methods: Nationwide surveillance of IPD for children <16 years in Germany was based on two independent reporting sources: active surveillance in paediatric hospitals and passive web-based surveillance through microbiological laboratories. Serotyping was performed using the Neufeld Quellung reaction. Case definition: isolation of *Streptococcus pneumoniae* from a normally sterile body site. IPD incidence was estimated by capture–recapture analysis. Rate ratios comparing post- to pre-vaccination incidence were calculated as well as PCV7 and non-PCV7 serotype specific incidences.
Results: While PCV7 incidence decreased by 88% (95%CI: 83 to 91) in children <16 years both in pneumococcal meningitis and non-meningitis IPD, an increase in Non-PCV7 serotypes was observed which was more pronounced in non-meningitis cases (168%; 95%CI: 140–257) than in pneumoccocal meningitis (65%; 95%CI: 23–123). The changes in incidence after four years were: <16 years: −35% (95%CI: −49 to −19), <2 years: −46% (95%CI: −61 to −27) for pneumococcal meningitis and + 11% (95%CI: −4 to +29) and −26% (95%CI: −41 to −7) for non-meningitis IPD respectively.
Conclusion: Infant PCV7 vaccination in Germany prompted a decrease in the incidence of pneumococcal meningitis similar to that observed in England/Wales. In non-meningitis IPD the decrease was smaller and confined to the age group <2 years with no change or an increase in incidence in other age groups pointing to potential ascertainment bias due to increased blood-culturing.

1. Introduction

In the United States (US) a seven-valent pneumococcal conjugate vaccination programme for children introduced in February 2000 prompted a dramatic decline in invasive pneumococcal disease (IPD) in vaccinated young children as well as in non-vaccinated adults and the elderly [1]. Meanwhile, pneumococcal infant vaccination has been implemented in several European countries [2]. Reported results were heterogeneous with some (but not all) reporting similar reductions as in the US for children <5 years, but generally less impressive results than in the US in school age children and adolescents [3]. Nationwide surveillance to assess the impact of vaccination was implemented in few countries in Europe [4–9]. Apart from a recent study from England/Wales which corrected for potential changes in case ascertainment and covered four years after introduction of seven-valent pneumococcal conjugate vaccination (PCV7), [6] the follow-up time of most studies was limited to one year [1,4,5,7] and no information was provided about possible differences in meningitis and non-meningitis cases [4,5,7]. In Germany a significant reduction in the IPD incidence for children <2 years (45%) two years after the

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introduction of general pneumococcal vaccination for all children under two years was found. No distinction between meningitis and non-meningitis IPD was made in that study [10].

In Germany vaccination with conjugate vaccine was recommended for high-risk children in July 2001 with a 3 plus 1 schedule and doses at 2, 3, 4 months plus a booster dose at 11–14 months [11]. This recommendation was extended to all children in July 2006. A catch-up campaign for all children <2 years was not part of the recommendation [12]. PCV7 was the only conjugate vaccine available in Germany until April 2009 when a 10-valent conjugate vaccine (PCV10) was introduced. The launch of the 13-valent conjugate vaccine (PCV13) with a concomitant withdrawal of PCV7 accounted for a major switch to PCV13 in Germany as of December 2009.

The reported pre-vaccination incidence rates of pneumococcal meningitis (per 100.000) were somewhat lower in Germany than in the US and England/Wales (<2 years: US: 10.2 [13]; UK: 10.0 [14]; Germany: 7.1 [14]) while total IPD rates (comprising meningitis and non-meningitis cases) for hospitalized children in Germany (<2 years: 19.9; 2–4 years: 5.1; <5 years: 11.0) were considerably lower (US, <5 years: 31.4 [1]; England/Wales <2 years: 54.2 [6]; 2–4 years: 16.4 [6]) suggesting substantial under-ascertainment of non-meningitis IPD cases due to poor blood culturing practices in Germany. A survey in a major university hospital showed indeed that only 50% of all hospitalized children with fever of unexplained origin had a blood culture [15]. Therefore we decided to present data on invasive pneumococcal disease (IPD) in children (<16 years) in Germany from 2007 to 2010 compared to the pre-vaccination period separate for meningitis and non-meningitis IPD.

In order to correct for possible underreporting we implemented an elaborate nationwide surveillance system based on two independent data sources with capture–recapture analyses. Temporal trends on incidence and serotype distribution since the introduction of PCV7 were compared to baseline surveillance data before the use of the vaccine in Germany covering 1997–2001. The data offer the opportunity to assess the net impact of infant pneumococcal conjugate vaccination on IPD incidence in children and adolescents four years after the universal recommendation of the conjugate vaccine for all infants.

2. Materials and methods

2.1. Data sources

In Germany, nationwide surveillance of IPD for children <16 years is performed with two independent reporting sources [10,16,17]. All children's hospitals and all paediatric wards in general hospitals in Germany ($n = 423$) are actively contacted each month to report on IPD cases. The participation rate reaches >95%. This hospital-based source is managed by the German paediatric surveillance unit (ESPED) [18]. Data collection in the hospital surveillance system had been put on hold in 2003 because of stable numbers since its start in 1997 but was resumed in January 2007 following the recommendation for universal infant pneumococcal conjugate vaccination in Germany. The second source is a laboratory-based passive sentinel surveillance for IPD at all ages called PneumoWeb (www.rki.de/pneumoweb). It is operated by the Robert Koch Institute (RKI), which is the federal institution responsible for infectious disease control and prevention in Germany. A laboratory-based active reporting system which had been initiated by RKI in 1997 to cover all laboratories was switched to a web-based passive system open for any microbiological laboratory in 2007. Cases from this source can be sorted according to whether specimen were obtained from paediatric hospitals or paediatric wards in general hospitals. Only those were included in the analysis. Serotyping is performed by the German National Reference Centre for Streptococci in Aachen.

2.2. Case definition

Cases were children <16 years of age treated for IPD as inpatients in a paediatric hospital or paediatric ward in general hospitals in Germany. IPD was defined as *Streptococcus pneumoniae* isolated from at least one culture of blood, cerebrospinal fluid, or a sample from any other normally sterile body site. Isolates from middle ear fluid were not included. Both surveillance sources (hospitals and laboratories) applied the same case definition.

2.3. Serotype microbiology and definition of vaccine coverage

Confirmation of the identities of the *S. pneumoniae* strains was performed by optochin sensitivity and bile solubility testing. Serotyping was performed by the Neufeld Quellung reaction using type and factor sera provided by the Statens Serum Institute, Copenhagen, Denmark. Serotypes were grouped into PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F), PCV10 serotypes (PCV7 serotypes plus 1, 5, 7F), and PCV13 serotypes (PCV10 serotypes plus 3, 6A, 19A). The serotyping rate went up from 34% in 1997 to 75% in 2010. IPD cases with unknown serotypes were distributed according to the percentages of serotypes among IPD cases with known serotypes.

2.4. Statistical analysis

IPD counts were estimated by capture–recapture calculation (CRC), which allows adjustment for incomplete reporting using overlapping lists of cases from different sources (from hospitals: collected by "ESPED" and from laboratories: collected by Pneumoweb"). The number of cases not included in either of the sources was estimated by applying Bayes' probability theory. Overlapping cases between the hospital- and the laboratory-based source were identified by four variables: date of hospital admission or respective date of specimen sampling, age in months, sex and postal code of the child's address (first three digits). We calculated the total number of IPD cases (N) and 95% confidence intervals (CI) using conventional CRC formulas [19]. The population denominator to convert the IPD estimates into incidence rates was based on age-specific population figures provided by the German Federal Statistical Office [20].

In order to assess the impact of the vaccination programme, incidence rate ratios (IRR) were calculated by dividing annual incidence rates post introduction of vaccination by the average incidence rates during pre-vaccination years from 1997 to 2001. A rate ratio of 1 indicates no effect of the vaccination programme. Rate ratios <1 show declining incidences, rate ratios >1 indicate rising incidences. The 95% confidence intervals for the IRR were calculated using the method described by Armitage and Berry [21].

All analyses were separately performed for meningitis and non-meningitis cases.

3. Results

3.1. Incidence in relation to the pre-vaccination period for pneumococcal meningitis

During the first four years following the introduction of pneumococcal conjugate vaccine in Germany there was a 35% (95%CI: 19 to 49) decrease (1-IRR) in the incidence of pneumococcal meningitis in children <16 years from 1.5/100,000 during 1997 to 2001 (= pre-vaccination) to 0.9/100,000 in 2010. This decrease was mainly