**CHILDHOOD DEATHS ATTRIBUTABLE TO INVASIVE PNEUMOCOCCAL DISEASE IN ENGLAND AND WALES, 2006-2014**

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In England and Wales, the childhood pneumococcal conjugate vaccination programme was associated with a 69% reduction in IPD-related mortality rates in children aged <5 years, with nearly all IPD-related childhood deaths now due to non-vaccine serotypes or in neonates

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**Abstract**

**Background**: Pneumococcal conjugate vaccines (PCV) are highly effective in preventing invasive pneumococcal disease (IPD) but deaths due to IPD still occur. We aimed to describe children who died of IPD since PCV introduction in England and Wales.

**Methods**: Public Health England conducts enhanced IPD surveillance in England and Wales. IPD cases in PCV-eligible children aged <5 years (born since 04 September 2004 and diagnosed between 04 September 2006 and 03 September 2014) were actively followed-up by postal questionnaires and, for fatal cases, detailed information was requested prospectively from multiple sources.

**Results**: During the 8-year period, there were 3,146 IPD cases and 150 IPD-related deaths (case fatality rate, 4.8%). Overall, 132 isolates from fatal cases were serotyped (88%) and 35 distinct serotypes were identified, with no serotype predominance. Most deaths occurred in <1 year-olds (88/150, 59%) and one year-olds (36/150, 24%). One-third (53/150, 35%) had a known risk factor for IPD. Clinical presentation varied with age but not by serotypes in the different conjugate vaccines. Meningitis was diagnosed in nearly half the fatal cases (71/150, 47%). IPD-related mortality-rate declined after PCV7 introduction from 1.25/100,000 children in 2006/07 to 0.60/100,000 in 2009/10, with a further reduction following PCV13 introduction from April 2010 to 0.39/100,000 in 2013/14 (14 deaths; IRR, 0.31; 95%CI, 0.16-0.61; P=0.0003), when most deaths were due to non-vaccine serotypes or in neonates.

**Conclusions:** Most fatal IPD cases are currently not vaccine-preventable. Additional strategies will be required to reduce childhood pneumococcal deaths in countries with established pneumococcal vaccination programmes.

**Introduction**

*Streptococcus pneumoniae* is a major cause of bacterial meningitis, septicemia and pneumonia, and is responsible for almost a million childhood deaths worldwide, with 11% of all deaths occurring in <5 year-olds (1). In England and Wales, prior to routine vaccination, the incidence of invasive pneumococcal disease (IPD) was highest in <2year-olds (36/100,000 in 2005/6) and the serotypes included in the 7-valent pneumococcal conjugate vaccine (PCV7) were responsible for 73% of IPD (2)

The United Kingdom introduced PCV7 into the routine childhood immunization schedule on 04 September 2006, at 2 and 4 months, with a booster at 12-13 months (2). At the same time, a 12-month catch-up campaign was initiated for children up to 24 months of age (3) From 01 April 2010, a 13-valent vaccine (PCV13) replaced PCV7, which aimed to protect against six additional pneumococcal serotypes (4).

Both vaccines have been highly effective in preventing IPD caused by the vaccine serotypes across all age-groups through direct and indirect (herd) protection, which was achieved by reducing acquisition of carriage in toddlers and, consequently, interrupting transmission to older children and adults (4). The reduction in PCV-type IPD was offset by a small increase in IPD caused by non-vaccine serotypes (NVT) but, eight years after PCV7 introduction, there has been an 56% reduction in overall IPD incidence in England and Wales compared to the pre-PCV7 baseline (4).

In industrialized countries with established PCV programmes, IPD-related IPD in children are uncommon, with reported case fatality rates (CFR) of <5% (5), but increases in children with underlying diseases. Consequently, little is known about the children who die of IPD and whether the pneumococcal conjugate vaccines have had any impact on IPD-related deaths. This study aimed to describe the epidemiological and clinical characteristics of children who died of IPD during the first eight years after PCV introduction in England and Wales.

**Methods**

Public Health England (PHE) initiated enhanced IPD surveillance in vaccine-eligible children in England and Wales following the introduction of the PCV7 on 04 September 2006. National Health Service (NHS) laboratories in England and Wales routinely submit all invasive pneumococcal isolates to the PHE national reference laboratory (NRL) for confirmation and serotyping; currently, >90% of invasive isolates nationally are serotyped by the NRL (5). All children in the age-group targeted for vaccination (i.e. born since 04 September 2004 and diagnosed between 04 September 2006 and 03 September 2014) and aged <5 years at diagnosis are actively followed-up using postal questionnaires to the child’s general practitioner (GP) and hospital pediatrician, requesting information about vaccination history, co-morbidities, clinical presentation and outcomes of IPD. Case ascertainment in vaccine-eligible children has remained consistently high since PCV7 introduction because serotyping of invasive isolates has direct impact on clinical management, because of its critical importance in identifying vaccine failure cases.

**Fatal cases**

Fatal cases were identified from the GP/clinician questionnaires, the Patient Demographic Service (a national database of NHS patients, <https://digital.nhs.uk/Demographics>) and electronic death registrations records provided by the Office for National Statistics (ONS, [www.statistics.gov.uk](http://www.statistics.gov.uk)) to PHE for surveillance purposes. For all fatal cases, the final hospital discharge summary, including the cause of death as recorded on the death certificate, was requested. In England and Wales all childhood deaths, including those who died outside the hospital, are referred to the coroner and subjected to a post-mortem, unless there was an irrefutable cause of death at the time of reporting (e.g. a child with pneumococcal meningitis who died in hospital). For fatal cases undergoing post-mortem examination, the coroner was contacted for the post-mortem report, which also contained the cause of death. Deaths were considered to be IPD-relatedif a child had a pure growth of *S. pneumoniae* isolated within 30 days from a normally sterile site before or after death, with clinical, radiological and/or histo-pathological evidence of invasive bacterial infection and after other differential diagnoses were appropriately excluded. Children with IPD who survived their infection and later died of other cases were excluded from the analysis, as were stillbirths and septic abortions.

Meningitis was defined as *S. pneumoniae* identified (culture/PCR) in the CSF or *S. pneumoniae* cultured from blood with radiological and/or clinical features of meningitis. Lower respiratory tract infection (LRTI) was defined as *S. pneumoniae* identified in pleural/empyema fluid or in blood with a radiological and/or clinical diagnosis of pneumonia. Septicemia was defined as *S. pneumoniae* cultured in blood with no clear focus of infection. Co-morbidity was defined as presence of a high-risk condition as defined in the Green Book on Immunization (6).

Cases were classified into 4 vaccine groups according to serotype: PCV7 serotypes (4,6B, 9V,14,18C,19F,23F), additional PCV13 serotypes (1,3,5,6A,7F,19A), non-PCV13 serotypes and unknown serotypes (typically due to non-referral, or unsuccessful recovery after transport to the NRL).

**Data Analysis**

Annual IPD-related mortality rates were calculated by dividing the number of IPD-related deaths in the vaccine-eligible cohort for each surveillance year with population estimates for the vaccine-eligible cohort in that year. Surveillance years were defined from 04 September to 03 September of the following year. Population denominators were obtained from the ONS. The vaccine-eligible cohort increased from three birth cohorts in 2006/07 to five in 2008/09 and subsequent years. Children aged 5 years were not routinely followed-up with detailed questionnaires and, therefore, not included in the analysis. Anonymized data were exported to Stata™ v.11.0 (Statcorp, Texas) for analysis, which were mainly descriptive. Categorical variables were described as percentages with binomial 95% confidence intervals (CI) and compared using the chi-squared test or Fisher Exact test. Continuous variables that did not follow a normal distribution were described as medians with interquartile ranges (IQR) and compared using the Mann-Whitney U test.

**Results**

During 04 September 2006 and 03 September 2014 (8 surveillance years, 10 birth cohorts), there were 3,146 children with *S. pneumoniae* isolated from a normally sterile site in England and Wales, including 222 fatalities. Of these, 72 deaths (32%) were excluded because they were not IPD-related; notably, 39 (54%) had sudden unexpected death in infancy (SUDI) recorded on their death certificate after post-mortem examination (**Figure 1**). The SUDI cases had a median age of 3 months (IQR, 1.5-10.5 months) and 26% (10/39) had been born prematurely. Most SUDI cases (34/39, 87%) had *S. pneumoniae* isolated from a post-mortem lung swab but with no histopathological evidence of pulmonary infection.

There were, therefore, 150 IPD-related deaths (CFR, 4.8%; 95% CI, 4.1-5.7%), including 50 (33%) who underwent post-mortem examination. The median age at death was 8 months (IQR, 1.3-17.8 months) and 79 (53%) were male. IPD-related fatalities were more common during the winter months, with 59 deaths (39%) occurring during November-February, compared to 17 (11%) during June-August. More than half the deaths (88/150, 59%) occurred in <1 year-olds and declined with age (**Table 1**). Most children were White (117/150, 78%) followed by Asian (20/150, 13%) and Black Afro-Caribbean (13/150, 9%). Two-thirds of children (96/150, 64%) died in the hospital, while one died in a hospice after suffering severe complications following pneumococcal meningitis. The remaining 53 died at home (n=20), on the way to the hospital (n=8) or in the Emergency Department (n=25) (**Table1**). There were no significant differences between these groups in terms of age, serotype group distribution, or comorbidity prevalence, but meningitis was more prevalent among children who died in hospital (55/96 [57%] vs. 17/53 [32%]; P=0.003).

**Serotypes**

Of the 132 (88%) serotyped isolates, 35 distinct serotypes were identified, with no serotype predominance (**Supplement Table S1)**. PCV7-serotypes were associated with 23/132 (17%) deaths with known serotype, of which 43% (10/23) occurred in the first year after PCV7 introduction. PCV7 serotypes were responsible for only 3/14 (21%) deaths in 2013/14.

The additional six PCV13 serotypes were responsible for 45 (34%) deaths, accounting for 23% (5/22) of deaths in 2006/07, 60% (12/20) in 2009/10 when PCV13 was introduced and none in 2013/14. The responsible serotypes were 19A (n=4), 3 (n=3), 1 (n=2), 7F (n=2), and 6A (n=1).

The non-PCV13 serotypes were responsible for 49% (64/132) of deaths overall and 73-92% of all IPD-related deaths after PCV13 introduction. The main serotypes were 23B (n=6), 22F (n=5), 24F (n=5), 33F (n=5), 6C (n=5), 8 (n=5), 38 (n=5), 15B (n=4), 15C (n=4), 11A (n=4).

**Vaccination-status**

Of the 112 children in the age-group eligible for vaccination, only 72 (64%) had been appropriately immunized according to their age, including 5/17 (29%) PCV7-eligible children who died of PCV7-type IPD and 26/32 (81%) PCV13-eligible children who died of PCV13-type IPD. Vaccine uptake was lowest in those eligible for the initial PCV7 catch-up for <2 year-olds (10/25, 40%) compared to those eligible for routine PCV7 (32/46, 70%) and PCV13 (30/41, 73%).

**Mortality Rate**

Annual IPD-related mortality rate in PCV eligible children over the 8-year period was 0.58/100,000 children, including 0.59/100,000 in boys and 0.56/100,000 in girls. IPD-related mortality rate declined from 1.25/100,000 (2006/07) to 0.60/100,000 (2009/10) after PCV7 introduction and 0.31/100,000 (2012/13) following PCV13 introduction (**Figure 2**). In 2013/14, the IPD-related mortality rate in <5 year olds was 0.39/100,000 (n=14; incidence rate ratio compared to 2006/7, 0.31; 95% CI, 0.16-0.61; P=0.0003)**.** Three deaths were due to PCV7 serotypes, including two infants with serotype 19F IPD who were too young to be immunized and one fully immunized toddler with serotype 14 IPD an asplenia diagnosed at post-mortem. Eight other deaths (two neonates, aged 1-11 months and 3 older children) were due to NVT, with no serotype predominance, and four (50%) had underlying comorbidities.

**Clinical Presentation**

Of the 150 IPD-related deaths, meningitis was the most common clinical presentation (n=71, 47%), followed by bacteremic pneumonia (n=43, 29%) and septicemia (n=36, 24%) (**Table1**). Notably, the clinical presentation did not vary by vaccine group (**Figure 3**).

**Co-morbidities**

A third (53/150, 35%) of children had an underlying co-morbidity, which did not vary with age (range, 30-50%). The main comorbidities included premature birth, (n=18, 12%; including 5/18 [28%] who had been born at <32 weeks gestation), especially in children who developed IPD in the first year of life, and congenital heart disease (9%, n=13). The range of different co-morbidities increased with age (**Table 1**).

Comorbidity prevalence was lower for PCV7 (4/24, 17%) and additional PCV13 (12/45, 27%) serotypes compared to other (29/64, 45%) and unknown serotypes (8/18, 44%; *P=0.035)*, but was not significantly different by diagnosis: meningitis (21/71, 30%), pneumonia (17/43, 40%) or septicemia (15/37, 41%; *P=0.41).*

In infants (<1 year-olds), nearly half the deaths (42/88, 48%) occurred in <3 month-olds, including 20 with early onset (EO) disease (0-6 days old). Five infants with EO-disease (25%) had been born prematurely with no other significant co-morbidities, while eight infants with late-onset (LO, age 7-89 days) disease had co-morbidities (8/22, 36%), including premature birth only (n=6), chromosomal disorder (n=1) and chronic respiratory disease (n=1). Clinical presentation also did not vary significantly between EO and LO deaths for meningitis (40% vs. 55%), septicemia (25% vs. 18%) or bacteremic pneumonia (35% vs. 27%). The serotype distribution was also unremarkable; in 2013/14, of the three EO and two LO fatalities, one each (both 19F) was due to a PCV serotype.

**Discussion**

In England and Wales, IPD in young children is rarely associated with a fatal outcome, with only 150 reported deaths in ten birth cohorts over eight surveillance years. The overall CFR was 4.8%, with 59% of deaths occurring in infants, mainly <3 month olds (28%), who were too young to benefit from the infant immunization programme. Overall, 35% had an underlying risk factor for IPD, mainly premature birth (12%) and congenital heart disease (9%). Meningitis was responsible for 47% of IPD-related fatalities and, remarkably, clinical presentation did not vary by vaccine group. PCV introduction was associated with a 69% reduction in IPD-related mortality in children aged <5 years since the first year of the immunization programme. The actual reduction is likely to be greater if we had been able to compare with pre-PCV7 rates. Currently, nearly all deaths are due to serotypes that are not included in the licensed PCVs.

Population based studies have consistently reported significant reductions in vaccine-type IPD after PCV7, PCV10 or PCV13 introduction (7). Replacement disease with non-vaccine serotypes occurs, but the reduction in overall IPD rates remains positive (7).

There are nearly 100 serologically distinct pneumococcal serotypes, each with different propensities for carriage, disease, clinical presentation, disease severity and death (7, 8, 9, 10, 11). In older children and adults at least, several vaccine and non-vaccine serotypes have been associated with more severe disease and death (12, 13). It is, therefore, not surprising that the changes in serotypes causing IPD following the introduction of two highly immunogenic PCVs would affect disease characteristics and outcomes. PCVs were developed to protect against the most virulent serotypes and it was hoped that any replacing serotypes would have lower invasive potential. This assertion is partly true in that non-vaccine serotypes have only partly replaced the large niche left by the PCV serotypes (4). In Spain, significant declines in IPD-related mortality rates have been reported in adults following both PCV7 and PCV13 introduction (14). In children, such impact has been more difficult to demonstrate because of the small number of childhood cases and deaths. Whilst confirming the low CFR in children with IPD, we also found a measurable decline in IPD-related childhood mortality after both PCV7 and PCV13 introduction.

A remarkable finding in our study was the consistency of clinical presentations with the different vaccine groups among fatal cases. After PCV7 introduction in England and Wales, an increase in the additional PCV13 and other serotypes was observed (3), along with an increase in LRTI presentations and a decrease in the other presentations (15), yet nearly half the IPD-related deaths remained due to meningitis, irrespective of the vaccine group responsible. Population-based studies have identified significant associations between pneumococcal serotypes and death among patients presenting with septicemia (12)and pneumonia (13) but not with meningitis (11, 13). This contrasts with experimental animal models of meningitis, where serotype-specific differences in survival, brain damage and inflammatory responses have been observed (16, 17). In the US, a recent study found that the number of children with pneumococcal meningitis did not change after PCV13 replaced PCV7, and there were no significant differences in presenting features, laboratory parameters, CSF findings, intensive care requirement, mechanical ventilation, neurosurgery, complications or death, even though the proportion of cases due to PCV13 serotypes halved after PCV13 introduction (18). The authors also found similar sequelae rates among survivors of PCV13 and non-PCV13 meningitis (18).

Reports of PCV7 and PCV13 impact on the incidence of childhood pneumococcal meningitis have been variable, with some regions finding significant reductions, while others reporting no measurable impact, partly because this is a rare disease with small numbers of cases, even in population-based studies (17, 18, 19, 20, 21). It is likely that, while PCVs may have an impact on circulating pneumococcal serotypes, once pneumococcal meningitis develops, the clinical course and outcomes are less dependent on the responsible serotype and more on host-related factors.

A major risk factor for death in children with IPD is the presence of underlying co-morbidities. We have previously reported that, following PCV7 introduction, clinical presentation with meningitis and the presence of co-morbidity were independent risk factors for death in children with IPD (15). IPD-related CFR was 8.5% in children with co-morbidities compared with 3.5% in those without (15). One third of our fatal cases had an underlying co-morbidity compared to an overall prevalence of 15% among children with IPD after PCV7 introduction, where malignancy/immunosuppression and congenital heart disease predominated (15). In <3 month-olds, we previously reported meningitis to be the only independent risk factor for death (22).

We also found lower immunization uptake among our fatal cases when compared to national coverage for children of a similar age (23), possibly reflecting poor utilization of the free healthcare service and potentially contributing to delayed presentation to hospital during the acute illness. The higher comorbidity prevalence among fatal cases may also have contributed to delayed immunization and the poor outcomes. It is, however, reassuring to note that overall cases and deaths due to vaccine serotypes have declined. In 2013/14, the three deaths related to PCV7 serotypes occurred in infants who were too young to be immunized or in those who had an underlying high-risk co-morbidity. These cases, however, do indicate that PCV7 serotypes continue to circulate in England and Wales, *albeit* at low rates. Among the NVT fatalities, no particular serotype predominated after PCV13 introduction; indeed, many of these serotypes have emerged among IPD cases only after PCV introduction (4).

The strength of this study lies in the prospective national follow-up of all children with IPD in the vaccine-eligible cohort, with high case ascertainment and questionnaire completion rates, along with detailed multi-source data for fatal cases, including post-mortem reports and death registration records. Since so few children die of IPD, it is important that all fatal cases are identified and thoroughly followed-up, preferably in a large population cohort and over a long period of time. The low CFR is reassuring but the small numbers mean that any observed differences and trends must be interpreted with caution. We also have no data childhood deaths prior to PCV7 introduction for comparison, or on long-term complications in IPD survivors, especially those with meningitis.

Nonetheless, there are important lessons to be learnt. PCV13-type IPD and PCV13-related deaths are currently rare and should continue to decline with the on-going childhood immunisation programme. Currently, most IPD-related childhood deaths are due to non-PCV13 serotypes or occur in infants too young to be protected through vaccination, suggesting that additional strategies will be required. In particular, more than 10% of deaths occurred in the first week of life, where perinatal transmission is likely to have occurred (22). *S. pneumoniae* is an uncommon but recognized cause of puerperal sepsis, with significant maternal and infant morbidity and mortality (24), as evidenced by the stillbirths and septic abortions identified in our surveillance, where *S. pneumoniae* was isolated from a normally sterile site at post-mortem **(Figure 1**). Unlike group B streptococci (GBS), however, *S. pneumoniae* rarely (<1%) colonizes the female genital tract but has a very high infant invasion to maternal colonization ratio (22). Clinicians should, therefore, consider empiric antibiotic treatment if they identify pregnant women with genital tract colonisation or neonatal colonisation at birth (25). The finding that more than one third of children (mainly infants) died outside the hospital or in the Emergency Department suggests either a very rapid onset or parental failure to recognize the warning symptoms and signs of serious infection. Raising awareness may improve earlier recognition of the sick child leading to earlier treatment, with better outcomes.

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**Ethical Approval**

PHE has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases (<http://www.legislation.gov.uk/uksi/2002/1438/regulation/3/made>). This includes PHE’s responsibility to monitor the safety and effectiveness of vaccines.

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**Conflicts of interest**

No external funding was received for this piece of work. SC, NA and SNL have provided vaccine manufactures with post-marketing surveillance reports, which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. In accordance with PHE policy a cost recovery charge is made for these reports payable to the Immunisation department. Public Health England has received payment for lectures given by RB from GSK, Baxter, SPMSD, and Novartis. MPES has received funding from Pfizer, GSK and Sanofi Pasteur for participation in Advisory Boards and from GSK and Astra Zeneca for participation in Symposia at International Scientific Meetings. RB and SNL perform contract research on behalf of Public Health England for GSK, Novartis, Pfizer and Sanofi Pasteur but receive no personal remuneration.

**References**

1. O’Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet 2009;374(9693):893–902.

2. Johnson AP, Waight P, Andrews N, Pebody R, George RC, Miller E. Morbidity and mortality of pneumococcal meningitis and serotypes of causative strains prior to introduction of the 7-valent conjugant pneumococcal vaccine in England. J Infect. 2007;55(5):394–9.

3. Miller E, Andrews NJ, Waight PA, Slack MPE, George RC. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: An observational cohort study. Lancet Infect Dis. 2011;11(10):760–8.

4. Waight PA, Andrews NJ, Ladhani SN, Sheppard CL, Slack MPE, Miller E. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: An observational cohort study. Lancet Infect Dis. 2015;15(5):535–43.

5. Navarro-Torné A, Dias JG, Hruba F, Lopalco PL, Pastore-Celentano L, Amato Gauci AJ, et al. Risk factors for death from invasive pneumococcal disease, europe, 2010. Emerg Infect Dis. 2015;21(3):417–25.

6. Salisbury D, Ramsay M, Noakes K. (updated 2013;11). Immunisation against infectious disease, 2006. The Stationary Office. <http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917> Accessed 10 March 2017

7. Hausdorff WP, Hanage WP. Interim results of an ecological experiment — Conjugate vaccination against the pneumococcus and serotype replacement. Vol. 12, Human Vaccines and Immunotherapeutics. 2016. p. 358–74.

8. Martens P, Worm SW, Lundgren B, Konradsen HB, Benfield T. Serotype-specific mortality from invasive Streptococcus pneumoniae disease revisited. BMC Infect Dis. 2004;4:21.

9. Flasche S, van Hoek AJ, Sheasby E, Waight P, Andrews N, Sheppard C, et al. Effect of pneumococcal conjugate vaccination on serotype-specific carriage and invasive disease in England: A cross-sectional study. PLoS Med. 2011;8(4):14.

10. Pichon B, Ladhani SN, Slack MPE, Segonds-Pichon A, Andrews NJ, Waight PA, et al. Changes in molecular epidemiology of Streptococcus Pneumoniae causing meningitis following introduction of pneumococcal conjugate vaccination in England and Wales. J Clin Microbiol. 2013;51(3):820–7.

11. Alanee SRJ, McGee L, Jackson D, Chiou CC, Feldman C, Morris AJ, et al. Association of serotypes of Streptococcus pneumoniae with disease severity and outcome in adults: an international study. Clin Infect Dis. 2007;45:46–51.

12. Harboe ZB, Thomsen RW, Riis A, Valentiner-Branth P, Christensen JJ, Lambertsen L, et al. Pneumococcal serotypes and mortality following invasive pneumococcal disease: a population-based cohort study. PLoS Med. 2009;6(5):e1000081–e1000081.

13. Weinberger DM, Harboe ZB, Sanders EAM, Ndiritu M, Klugman KP, Rückinger S, et al. Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. Clin Infect Dis. 2010;51(6):692–9.

14. Grau I, Ardanuy C, Cubero M, Benitez MA, Liñares J, Pallares R. Declining mortality from adult pneumococcal infections linked to children’s vaccination. J Infect. 2016;72(4):439–49.

15. Ladhani SN, Slack MPE, Andrews NJ, Waight PA, Borrow R, Miller E. Invasive pneumococcal disease after routine pneumococcal conjugate vaccination in children, England and Wales. Emerg Infect Dis. 2013;19(1):61–8.

16. Østergaard C, Brandt C, Konradsen HB, Samuelsson S. Differences in survival, brain damage, and cerebrospinal fluid cytokine kinetics due to meningitis caused by 3 different Streptococcus pneumoniae serotypes: evaluation in humans and in 2 experimental models. J Infect Dis. 2004;190(7):1212–20.

17. Engelhard D, Pomeranz S, Gallily R, Strauss N, Tuomanen E. Serotype-related differences in inflammatory response to Streptococcus pneumoniae in experimental meningitis. J Infect Dis. 1997;175(4):979–82.

18. Olarte L, Barson WJ, Barson RM, Lin PL, Romero JR, Tan TQ, et al. Impact of the 13-Valent Pneumococcal Conjugate Vaccine on Pneumococcal Meningitis in US Children. Clin Infect Dis. 2015;61(5):767–75.

19. Hsu HE, Shutt KA, Moore MR, Beall BW, Bennett NM, Craig AS, et al. Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. N Engl J Med. 2009;360(3):244–56.

20. Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, et al. Bacterial Meningitis in the United States, 1998-2007 (English). N Engl J Med. 2011;364(21):2016–25.

21. Levy C, Varon E, Picard C, Béchet S, Martinot A, Bonacorsi S, et al. Trends of pneumococcal meningitis in children after introduction of the 13-valent pneumococcal conjugate vaccine in france. Pediatr Infect Dis J. 2014;33(12):1216–21.

22. Ladhani SN, Andrews NJ, Waight P, Borrow R, Slack MPE, Miller E. Impact of the 7-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in infants younger than 90 days in England and wales. Clin Infect Dis. 2013;56(5):633–40.

23. Public Health England. Vaccine uptake guidance and the latest coverage data. Available at: https://www.gov.uk/government/collections/vaccine-uptake. Accessed: 01 March 2017.

24. Deutscher M, Lewis M, Zell ER, Taylor TH, Van Beneden C, Schrag S. Incidence and severity of invasive streptococcus pneumoniae, group a streptococcus, and group b streptococcus infections among pregnant and postpartum women. Clin Infect Dis. 2011;53(2):114–23.

25. Hoffman JA, Mason EO, Schutze GE, Tan TQ, Barson WJ, Givner LB, et al. Streptococcus pneumoniae Infections in the Neonate. Pediatrics. 2003;112(5):1095–102.

Number of children aged <5years with IPD diagnosed during 04 Sept 2006 and 03 Aug 2014: 3,146

Number of children who died of IPD

N = 222

Number survived IPD

N = 2,924

Number of IPD-related deaths

N = 150

Number excluded after post-mortem and coroner’s report: N = 72

1. SUDI = 39
2. Other Diagnosis\* = 12
3. Born Abroad = 12
4. Survived IPD but died later \*\* = 7
5. Duplicate = 2

**Figure 1: Flow Chart of IPD Deaths in Children < 5years old in England and Wales, September 2006 – August 2014.**

*\* Twelve children died of other causes, including group A streptococcal disease (n=2), traumatic head injury (n=2), aspiration pneumonia (n=2), enterococcal meningitis, septic abortion following maternal chorioamnionitis, stillbirth following intra-uterine hypoxia due to maternal infection, cardiomyopathy, rotavirus gastro-enteritis and non-accidental Injury.*

*\*\* the cause of death in children who survived IPD but died later of another cause included one case each of Escherichia coli septicemia, varicella pneumonia, haemorrhagic shock following bowel obstruction, chronic liver disease, meningococcal septicemia, group A streptococcal septicemia,*

**IPD=Invasive pneumococcal disease; SUDI=Sudden Unexpected Death in Infancy.**

**Figure 2: Incidence of IPD Deaths in children aged <5 years in England and Wales, September 2006 to August 2014.**

PCV7 = serotypes included in the 7-valent pneumococcal conjugate vaccine; PCV13 = additional 6 serotypes included in the 13-valent pneumococcal conjugate vaccine; Other = serotypes not included in the 13-valent pneumococcal conjugate vaccine; Not Known = serotypes not known because isolates not serotyped

**Figure 3: Proportion of IPD deaths with clinical presentation by serotype group in children aged <5 years with laboratory-confirmed IPD in England and Wales, September 2006 to August 2014.**

PCV7 = serotypes included in the 7-valent pneumococcal conjugate vaccine (23 cases); PCV13 = additional 6 serotypes included in the 13-valent pneumococcal conjugate vaccine (45 cases); Other = serotypes not included in the 13-valent pneumococcal conjugate vaccine (64 cases); NK = serotypes not known because isolates not serotyped (18 cases)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **<1 month**  **(n=27, 18%)** | **1-5 months**  **(n=34, 23%)** | **6-11 months**  **(n=27, 18%)** | **1y**  **(n=35, 23%)** | **2-4y**  **(n=27, 18%)** | **Total**  **(n=150, 100%)** |
| **Gender** |  |  |  |  |  |  |
| Male | 13(48.1) | 20(58.8) | 14(51.9) | 17(48.6) | 15(55.6) | 79(52.7) |
| **Serotypes Group** |  |  |  |  |  |  |
| **PCV7 serotypes** | 4 (15%) | 6 (18%) | 4 (15%) | 7 (20%) | 2 (7%) | 23 (15%) |
| **Additional PCV13 serotypes** | 10 (37%) | 10 (29%) | 9 (33%) | 8 (23%) | 8 (30%) | 45 (30%) |
| **Non-PCV13 serotypes** | 10 (37%) | 14 (41%) | 13 (48%) | 14 (40%) | 13 (48%) | 64 (43%) |
| **Serotype not known** | 3 (11%) | 4 (12%) | 1 (4%) | 6 (17%) | 4 (15%) | 18 (12%) |
| **Comorbidity status** |  |  |  |  |  |  |
| No Comorbidity | 21(77.8) | 20(58.8) | 16(59.3) | 25(71.4) | 15(55.6) | 97(64.7) |
| Any Comorbidity | 6(22.2) | 14(41.2) | 11(40.7) | 10(28.6) | 12(44.4) | 53(35.3) |
| Prematurity | 5(18.5) | 5(14.7) | 7(26) | 1(2.9) | 0(0) | 18(12) |
| Chronic Heart Disease | 0(0) | 5(14.7) | 2(7.4) | 3(8.6) | 3(11.1) | 13(8.7) |
| Asplenia | 0(0) | 0(0) | 1(3.7) | 2(5.7) | 2(7.4) | 5(3.3) |
| Immunosuppression | 0(0) | 0(0) | 0(0) | 2(5.7) | 3(11.1) | 5(3.3) |
| Neurodevelopmental disorder | 0(0) | 1(2.9) | 1(3.7) | 0(0) | 3(11.1) | 4(2.6) |
| chromosomal disorder | 1(3.7) | 1(2.9) | 0(0) | 1(2.9) | 1(3.7) | 4(2.6) |
| Chronic Respiratory Disease | 0(0) | 1(2.9) | 0(0) | 1(2.9) | 1(3.7) | 3(2) |
| Chronic Liver Disease | 0(0) | 1(2.9) | 0(0) | 0(0) | 0(0) | 1(0.6) |
| **Clinical Presentation** | |  |  |  |  |  |
| Meningitis | 12(44.4) | 17(50) | 16(59.2) | 14(40) | 12(44.4) | 71(47.3) |
| Pneumonia | 7(26) | 11(32.4) | 2(7.4) | 13(37.1) | 10(37) | 43(28.7) |
| Septicaemia | 8(29.6) | 6(17.6) | 9(33.3) | 8(22.9) | 5(18.5) | 36(24) |
| **Place of Death** | |  |  |  |  |  |
| Home | 2(7.4) | 7(20.6) | 1(3.7) | 7(20) | 3(11.1) | 20(13.3) |
| En route to the hospital | 1(3.7) | 0(0) | 2(7.4) | 1(2.9) | 4(14.8) | 8(5.5) |
| Emergency Department | 3(11.1) | 9(26.5) | 5(18.5) | 5(14.3) | 3(11.1) | 25(16.7) |
| Ward | 2(7.4) | 3(8.8) | 3(11.1) | 6(17.1) | 1(8.3) | 15(10) |
| PICU | 10(37) | 13(38.2) | 16(59.2) | 16(45.7) | 16(59.3) | 71(47.3) |
| NICU | 9(33.3) | 1(2.9) | 0(0) | 0(0) | 0(0) | 10(6.7) |
| Hospice | 0(0) | 1(2.9) | 0(0) | 0(0) | 0(0) | 1(0.6) |

Table 1. **Characteristics of IPD death cases in children <5 year olds in England and Wales between 04 September 2006 to 03 August 2014).** PICU = paediatric intensive care unit, NICU = neonatal intensive care unit

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Surveillance year** | | | | | | | | |
|  | **Sep06/Aug07** | **Sep07/Aug08** | **Sep08/Aug09** | **Sep09/Aug10** | **Sep10/Aug11** | **Sep11/Aug12** | **Sep12/Aug13** | **Sep13/Aug14** | **Total** |
| **Total (%)** | 25(16.7) | 17(11.3) | 24(16) | 21(14) | 25(16.7) | 13(8.7) | 11(7.3) | 14(9.3) | **150(100)** |
| **Population at risk** | 2,005,467 | 2,714,178 | 3,420,424 | 3,497,754 | 3,552,066 | 3,591,709 | 3,581,510 | 3,570,497 | **25,933,596** |
| **Incidence per 100,000** | 1.25 | 0.63 | 0.7 | 0.6 | 0.7 | 0.36 | 0.31 | 0.39 | **0.58** |
| **Serotypes** | | | | | | | | | |
| **PCV7** | 10(40) | 2(11.8) | 2(8.3) | 3(14.3) | 1(4) | 1(7.7) | 1(9) | 3(21.4) | **23(15.4)** |
| **PCV13** | 5(20) | 6(35.3) | 10(41.7) | 12(57.1) | 11(44) | 0(0) | 1(9) | 0(0) | **45(30)** |
| **Additional PPV** | 3(12) | 4(25) | 4(16.7) | 1(4.8) | 1(4) | 5(38.5) | 3(27.3) | 5(35.7) | **26(17.3)** |
| **Non Vaccine Serotypes (NVT)** | 4(16) | 3(17.6) | 5(20.8) | 4(19) | 8(32) | 7(53.8) | 4(36.4) | 3(21.4) | **38(25.3)** |
| **Not Known (NK)** | 3(12) | 2(11.8) | 3(12.5) | 1(4.8) | 4(16) | 0 | 2(18.2) | 3(21.4) | **18(12)** |
| **PCV7 Serotypes** | | | | | | | | | |
| **19F** | 1 | 0 | 1 | 2 | 1 | 1 | 0 | 2 | **8** |
| **14** | **4** | 0 | 0 | 0 | 0 | 0 | 0 | 1 | **5** |
| **6B** | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | **3** |
| **18C** | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | **3** |
| **9V** | **2** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **2** |
| **23F** | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **1** |
| **4** | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | **1** |
| **PCV13 Serotypes** | | | | | | | | | |
| **3** | 0 | **4** | **2** | **3** | **4** | 0 | 0 | 0 | **13** |
| **19A** | 1 | 0 | **5** | **4** | **1** | 0 | 0 | 0 | **11** |
| **7F** | 2 | 0 | **1** | **2** | **3** | 0 | **1** | 0 | **9** |
| **1** | 1 | 1 | 1 | 2 | 2 | 0 | 0 | 0 | **7** |
| **6A** | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | **4** |
| **5** | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | **1** |
| **Additional PPV** | | | | | | | | | |
| **33F** | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | **5** |
| **8** | 0 | 0 | 1 | 0 | 0 | 1 | 2 | 1 | **5** |
| **22F** | 0 | 2 | 1 | 0 | 0 | 1 | 0 | 1 | **5** |
| **11A** | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | **4** |
| **15B** | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 2 | **4** |
| **17F** | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | **1** |
| **10A** | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | **1** |
| **12F** | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | **1** |
| **Non Vaccine Serotypes (NVT)** | | | | | | | | | |
| **23B** | 0 | 0 | 1 | 1 | 1 | 2 | 0 | 1 | **6** |
| **24F** | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | **5** |
| **6C** | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | **5** |
| **38** | 0 | 1 | 0 | 1 | 3 | 0 | 0 | 0 | **5** |
| **15C** | 0 | 0 | 0 | 1 | 1 | 2 | 0 | 0 | **4** |
| **15A** | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | **3** |
| **35B** | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | **2** |
| **35F** | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | **2** |
| **16F** | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | **1** |
| **31** | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | **1** |
| **27** | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | **1** |
| **23A** | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **1** |
| **22A** | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | **1** |
| **21** | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | **1** |
| **Serotypes Not Known (NK)** | 3 | 2 | 3 | 1 | 4 | 0 | 2 | 3 | **18** |
| **Total** | **25** | **17** | **24** | **21** | **25** | **13** | **11** | **14** | **150** |

**SUPPLEMENT TABLE S1. Serotype Distribution in IPD death cases in Children < 5 year olds by serotype group and year of death in England and Wales between 03 September 2006 to 04 August 2014**