**RISK OF INVASIVE PNEUMOCOCCAL DISEASE IN CHILDREN WITH SICKLE CELL DISEASE IN ENGLAND: a national observational cohort study, 2010 – 2015.**

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**ABSTRACT**

**OBJECTIVE:** To describe the clinical presentation, risk factors, serotype distribution and outcomes of invasive pneumococcal disease (IPD) in children with sickle cell disease (SCD) following the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) in the United Kingdom

**DESIGN:** Prospective national newborn screening for SCD and enhanced national IPD surveillance

**PARTICIPANTS:** Children with SCD born in England between 01 September 2010 and 31 August 2014 who developed laboratory-confirmed IPD by 31 December 2015

**MAIN OUTCOMES AND MEASURES:** Risk of IPD in children with SCD compared to children without SCD during the surveillance period

**RESULTS:** Eleven children homozygote for haemoglobin S (HbSS) and one double heterozygote for haemoglobin S and C (HbSC) developed IPD. Septicaemia (n=7) and lower respiratory tract infection (n=4) were the main clinical presentations and serogroup 15 (not present in PCV13) was responsible for 73% (8/11) of cases. Three children with HbSS (27%) died compared to <5% nationally. Children with HbSS had a 49-fold (95%CI, 27-89, p<0.001) higher risk of IPD compared to their peers without SCD.

**CONCLUSIONS:** Children with SCD remain at increased risk of IPD despite national newborn screening, early penicillin prophylaxis and high pneumococcal vaccine uptake. They are also more likely to die of their infection compared to their peers without SCD. Most IPD cases are now due to serotypes not covered by PCV13. Healthcare professionals need to work more closely with families with SCD and local communities to emphasise the importance of penicillin prophylaxis, explore barriers, allay misguided beliefs and facilitate rapid access to healthcare.

**What’s Known on This Subject?**

Pneumococcal conjugate vaccines (PCV) are highly effective at preventing invasive pneumococcal disease (IPD) across all age groups through direct and indirect (herd) protection.

The UK introduced the 7-valent PCV into the national childhood immunisation programme in 2006, which was replaced with the 13-valent PCV (PCV13) in April 2010.

In the pre-PCV era, children with sickle cell disease (SCD) had a >600-fold increased risk of IPD, with more severe disease and higher case fatality.

**What This Study Adds?**

In the PCV13 era, children with sickle cell disease (SCD) remain 49 times more likely to develop IPD and >5 times more likely to die of their infection.

Most IPD cases in children with SCD are due to pneumococcal serotypes that are not covered by PCV13.

Healthcare professionals must continue working closely with families and local communities to highlight the importance of long-term penicillin prophylaxis, and to facilitate rapid healthcare access

**Introduction**

Children with sickle cell disease (SCD) often have functional asplenia, with dysfunctional antibody production and poor opsonophagocytosis, making them susceptible to encapsulated bacteria, especially *Streptococcus pneumoniae*.1,2,3 In the absence of any intervention, children with SCD have a 600-fold higher risk of invasive pneumococcal disease (IPD) compared to their healthy peers.4 With penicillin prophylaxis and 23-valent pneumococcal polysaccharide vaccination, this risk is reduced substantially, although children with SCD continued to have a 10-100-fold higher risk of IPD, with reported case fatality rates of up to 15% in industrialised countries.5,6,7

Pneumococcal conjugate vaccines (PCVs) are highly immunogenic and provide robust antibody responses, even in children with comorbidities such as SCD.8,9 In the United States, routine childhood immunisation with the 7-valent PCV (PCV7) in 2000 was associated with a significant decline in IPD incidence among patients with SCD, especially in children aged <5 years.10,11 The 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in 2010 but its impact on IPD in children with SCD remains to be established. The United Kingdom introduced PCV7 in September 2006 at two, four and 12-13 months of age.12 This programme led to a rapid decline in PCV7-type and overall IPD across all age groups because of direct and indirect (herd) protection.13 In April 2010, PCV7 was replaced by a 13-valent PCV (PCV13) without any catch-up, to provide additional protection against some of the major replacing pneumococcal serotypes causing IPD.14

In 2006, a newborn bloodspot screening programme for SCD was also implemented in England.15 Prior to this, newborn screening was only available in some high prevalence regions.16 Recently, the newborn outcomes programme identified nine deaths in <5 year-olds with SCD, including three who died of IPD. We, therefore, undertook this study to describe the children with SCD who were identified through the national newborn screening programme and followed up as part of the national SCD screening programme, who developed IPD after PCV13 introduction, and to assess any additional risk compared with their peers without SCD, who developed IPD during the same surveillance period.

**Methods**

A national newborn screening programme for SCD was implemented across England between 2003-2006.17 SCD birth prevalence in England was estimated at 1 in 2,500 live births. To support implementation, standards for the programme (https://www.gov.uk/government/uploads/system/uploads/attachment\_data/file/402208/Standards2ndEdition1.pdf) and guidelines for the clinical care of children with SCD have been published.18 The latter recommend that infants with SCD should be referred to a specialist haemoglobinopathy team by eight weeks of age, and assessed and offered penicillin prophylaxis by three months. For this study, children with SCD were identified from the national newborn outcomes project, based at Kings College London between 2010 and April 2017 (and now based at National Congenital and Rare Disease registration service (NCARDS). The newborn outcomes study collects named patient data for all infants born in England with a screen positive result and follows-up infants with confirmed SCD to determine outcomes (https://www.gov.uk/government/publications/sickle-cell-and-thalassaemia-screening-outcome-data-collection-template). Since April 2010, all infants are routinely offered PCV13 and those at increased risk if IPD (including SCD) are also offered the 23-valent pneumococcal polysaccharide vaccine (PPV23) from two years of age.19

In England, Public Health England (PHE) conducts enhanced national surveillance of IPD, defined as *S. pneumoniae* cultured from a normally sterile site or pneumococcal DNA detected in cerebrospinal fluid (CSF) or pleural fluid. Briefly, hospital laboratories routinely report clinically significant infections to PHE electronically and submit invasive pneumococcal isolates to the PHE Reference Laboratory for confirmation and serotyping. For confirmed IPD in <5 year-olds, PHE routinely contacts general practitioners (GPs) to complete a short questionnaire on vaccination history, co-morbidities, risk factors, clinical presentation complications and outcomes of infection. Adherence to antibiotic prophylaxis in children with SCD was not formally assessed.

**Data Analysis**

Children born between 01 September 2010 to 31 August 2014 (four annual birth cohorts) in England and diagnosed with laboratory-confirmed IPD until 31 December 2015 were included in the analysis. IPD cases in children with SCD were identified through the national surveillance questionnaires and compared to cases without SCD. The prevalence of SCD in England was provided from the newborn outcomes project, which also identified three deaths following IPD in this cohort during this period. Data on numbers of births obtained from the office for national statistics were used to provide total population denominators. Age-specific childhood population rates were obtained from the Office for National Statistics (https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/adhocs/005962numberofhomebirthsandtotallivebirthsengland1994to2014). Population estimates for incomplete years were estimated by dividing the annual population in the defined age-group by the number of months of surveillance for that year. Data are mainly descriptive; categorical variables are described as percentages with binomial 95% confidence intervals (CI) and compared using the chi-squared test or Fisher exact test and continuous variables that did not follow a normal distribution are described as medians. Incidence rate ratios (IRR) with 95% CI were calculated using Poisson regression and used to estimate any additional risk of IPD in children with SCD compared to their peers without SCD. A p value of <0.05 was considered statistically significant.

**Results**

Between 01 September 2010 and 31 December 2015 (5 years and 4 months follow-up), there were 881 IPD cases in the four annual birth cohorts (born between 01 September 2010 and 31 August 2014) in England. Within this cohort, 12 cases in children with SCD were identified: 11 homozygote for haemoglobin S (HbSS) and one double heterozygote for haemoglobin S and C (HbSC).

Seven of the eleven HbSS cases with IPD were African (64%), and two each (18%) were Caribbean and mixed African/Caucasian. All were appropriately immunised with PCV13 and PPV23 for their age. The median age at IPD was 13 months, with the majority of cases (9/11, 82%) diagnosed before two years of age (Table 1) and serogroup 15 was most commonly responsible for IPD (8/11 cases, 73%). Two-thirds presented with septicaemia and a third with lower respiratory tract infection (LRTI); there were no cases of meningitis. All LRTI cases were diagnosed by two years of age and were due to serogroup 15. One child developed IPD due to a vaccine-preventable serotype; an infant with uncomplicated serotype 7F pneumococcal septicaemia at 3 months of age after a single infant PCV13 dose.

Of the two children with HbSS who developed IPD after their second birthday (2/11 cases, 18%), both were fully immunised with PCV13 and one had also received PPV23. The former developed IPD due to serogroup 15 and survived, while the latter developed IPD due to serotype 15B/C and died. Three children with HbSS, including two born prematurely, died of IPD – all due to serotype 15 B/C (case fatality rate [CFR], 27%); two had septicaemia and one had LRTI.

There was one additional case of IPD in a child with HbSC, who was fully immunised, developed IPD due to a serotype 33F (non-PCV13) in the second year of life and recovered uneventfully.

**Relative Risk of IPD**

The denominator for the study cohort (all children in England born between 01/09/2010 and 31/08/2014) was 2,716,879 children, and included 700 children with HbSS and 304 with HbSC; within this cohort, 11 children with HbSS and one with HbSC developed IPD. The risk of IPD in the defined birth cohort over the surveillance period was 32/100,000 children. This compares with 1,571/100,000 in children with HbSS, which is 49-fold (95% CI, 27-89, p<0.00001) higher compared to their age-matched peers without SCD. Similarly, a 10-fold (95% CI, 2-73; P=0.004) risk was identified in children with HbSC (329/100,000) higher compared to their age-matched peers without SCD.

**Discussion**

Our study highlights the case for a national screening programme to rapidly detect SCD after birth (a condition with persistently high morbidity and mortality even in industrialised countries) and the importance of vaccination and penicillin prophylaxis in children with SCD. We conducted this analysis after an excess of IPD-related deaths was identified during the long-term follow-up of children with SCD diagnosed through the evaluation of the national screening programme in England. We found a 49-fold increased risk of IPD in children with HbSS compared to their age-matched peers without SCD, during the period after PCV13 replaced PCV7 in 2010. This increased risk, however, is substantially lower than the >600-fold increased risk reported in the past.4 Nearly all the IPD episodes in children with SCD occurred in the first two years of life, which is not surprising because this age group struggles to mount protective antibodies against encapsulated bacteria such as the pneumococcus. Additionally, whilst it is reassuring that all the children with SCD and IPD had been appropriately immunised with PCV13 according to the nationally recommended schedule, nearly all cases were due to serotypes not included in PCV13. Only one case was due to a PCV13 serotype in a partially immunized infant. More concerning was the observation that three of the 11 children with HbSS died of their infection, despite all the pneumococcal strains being penicillin-sensitive.

The introduction of PCV7 into national childhood immunisation programmes had a greater than expected impact on IPD due to the PCV7 serotypes across all age groups.13 Those at increased risk of IPD (including SCD) benefited directly (through vaccination) and indirectly (through herd protection) from the programme. In the US, where PCV7 was introduced in the early 2000’s, the Active Bacterial Core surveillance reported a 53% decline in IPD rates among children with SCD during 1998-2009, which was lower than the 74% decline observed among African-American children without SCD.11 Moreover, children with SCD remained at significantly higher risk of IPD compared to their healthy peers. They were also more likely to be hospitalised and die of their infection compared to healthy children with IPD. Other US studies have also reported significant declines in IPD rates among children with SCD following PCV7 introduction.10,20

After PCV7 introduction, a number of reports emerged of IPD cases in children with SCD that were due to serotypes that were not covered by PCV7.21 The replacement of PCV7 with PCV13 in 2010 was timely because the latter vaccine provided protection against six additional serotypes. As yet, however, there are no published epidemiological studies on the impact of PCV13 on IPD in children with SCD.

In England, the rapid decline in PCV13 serotypes across all age groups following PCV13 introduction is well-documented.14 We were unable to undertake any trends analysis in our cohort of children with SCD because of the relatively few IPD cases. Our results, however, show that PCV13 serotypes are now rarely responsible for IPD in children with SCD, most likely because of the excellent direct and indirect protection offered by the current immunisation programme. Consequently, the majority of IPD cases in children (including those with SCD) are now due to serotypes not included in PCV13.14 Others have also reported a disproportionate proportion of IPD cases due to non-PCV serotypes in children with SCD compared to children without SCD after PCV7 (77% vs. 44% in one study),11 and –more recently – after PCV13.22 It is noteworthy that, after PCV7 introduction, 10 and after PCV13 introduction,23 serogroup 15 appears to be a particularly common cause of IPD among children with SCD, accounting for 73% of IPD cases in our cohort. Genomic analysis of invasive isolates and murine SCD studies have suggested that some pneumococcal strains may be particularly adapted to cause invasive disease in children with SCD.24

Whilst it is reassuring that there were no cases of meningitis (the most severe presentation of IPD) in our SCD cohort, the CFR of 27% in children with HbSS is much higher than that reported for overall childhood IPD (4.4%), IPD in children with co-morbidities (8.5%) and even pneumococcal meningitis (11.0%) in England and Wales.25 Moreover, two of the three IPD-related deaths occurred in infants who had been born prematurely, who are also known to be at increased risk of IPD.26

**Clinical Implications**

IPD due to PCV13 serotypes is now rare in UK children, even in high-risk groups such as those with SCD.14 Timely immunisation according to the nationally recommended schedule is vital to ensure that children with SCD are adequately protected against all vaccine-preventable diseases. In the UK, children with asplenia or splenic dysfunction, including those with SCD are recommended to also have PPV23 from two years of age and every five years thereafter, although it’s effectiveness in at-risk individuals remains under considerable debate. 27**,**28

More importantly, however, since PCV13-type IPD is now rare, our results therefore, highlight the importance of education and advising on the importance of strict adherence to penicillin prophylaxis, which will not only help protect against all pneumococcal infections but also against other encapsulated bacteria.29 The lack of penicillin resistance among pneumococcal isolates causing IPD in our cohort of children with SCD may suggest that these children were not adherent to penicillin prophylaxis at the time of infection. Nationally, surveillance of children with SCD found that 97% of children with SCD were prescribed penicillin prophylaxis by 6 months, with only 7 refusals during the follow-up period of this study. A recent systematic review found that compliance rates for long-term medications in children with SCD ranged from 16% to 89%.30 In addition to the difficulties in administering daily medication to young children and to lifestyle factors, such as forgetting to give the medication or to obtain refill prescriptions on time, poor compliance is also related to levels of parental knowledge, understanding and beliefs about safety and effectiveness of medications. Healthcare professionals need to continue to work closely with SCD families and local communities to emphasise the importance of prophylaxis, explore barriers, allay any misguided negative personal or religious beliefs about SCD and infections, and also to facilitate rapid access to healthcare, including penicillin prescriptions when requested.31 Moreover, national screening programmes for SCD should consider including objective assessments of compliance to penicillin prophylaxis when evaluating outcomes.30

**Strengths and Limitations**

The UK newborn screening programme has been highly successful in identifying children with SCD because of the high screening coverage achieved, with nearly all infants diagnosed before they developed their first symptoms. The well-established national IPD surveillance has been in place for more than two decades, with high case ascertainment due to a single national reference laboratory and near-complete follow-up of cases in <5 year-olds. This study also highlights the value of linking different national datasets to study rare outcomes in small cohorts, which is often limited by the lack of appropriate denominator data. Ideally, we would have liked to compare IPD rates in children with SCD to IPD rates in Afro-Caribbean children without SCD, and to children with and without co-morbidities. However, ethnicity is poorly reported and we do not have reliable national denominator data for children with different co-morbidities. It is also important to emphasise that, despite the high relative risk, there were only 12 children with SCD in England who developed laboratory-confirmed IPD over >5 follow-up years. Additionally, we did not formally assess compliance with penicillin prophylaxis, which is known to be highly protective against IPD, especially in countries such as the UK, where pneumococcal penicillin-resistance is rare.32

**Conclusions**

Children with SCD remain at increased risk of IPD in spite of all the current interventions, including newborn screening, early referral for long-term specialist care, recommendations for daily penicillin prophylaxis from three months of age and timely immunisation with high uptake rates. Given that most serotypes causing IPD in children with SCD are now no longer vaccine preventable, increased efforts must be made to improve uptake and adherence to penicillin prophylaxis. Further studies should assess whether improving parental education to seek early medical help might also achieve better outcomes. Our findings also highlight the need for higher valency PCV or, preferably, a universal vaccine targeting all pneumococci irrespective of their capsular serotype.33

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**Table 1: Characteristics of Children with Sickle Cell Disease (HbSS) born between 01 September 2010 and 31 August 2014 who developed Invasive Pneumococcal Disease (IPD) in England and Wales between September 2010 and 31 December 2015**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Characteristics** |  | **0-12 months** | **13-24 months** | **>2 years** | **Total** |
| N (%) |  | 4(36) | 5(46) | 2(18) | 11(100) |
| **Sex** |  |  |  |  |  |
|  | Male | 2(50) | 3(60) | 1(50) | 6(55) |
| **Ethnicity** |  |  |  |  |  |
|  | African | 3(75) | 3(60) | 1(50) | 7(64) |
|  | Caribbean | 1(25) | 1(20) | 0(0) | 2(18) |
|  | Mixed white/African | 0(0) | 1(20) | 1(50) | 2(18) |
| **Comorbidity** |  |  |  |  |  |
|  | Prematurity | 1(25) | 2(40) | 0(0) | 3(27) |
|  | Others | 0(0) | 0(0) | 0(0) | 0(0) |
| **Presentations** |  |  |  |  |  |
|  | Septicaemia | 2(50) | 3(60) | 2(100) | 7(64) |
|  | Pneumonia | 2(50) | 2(40) | 0(0) | 4(36) |
| **Serotypes** |  |  |  |  |  |
| ***PCV13*** | 7F | 1(25) | 0(0) | 0(0) | 1(9) |
|  |  |  |  |  |  |
| ***Non-PCV13*** | 15 | 0(0) | 0(0) | 1(50) | 1(9) |
|  | 15A | 1(25) | 1(20) | 0(0) | 2(18) |
|  | 15B/C | 1(25) | 3 (60) | 1(50) | 5(45) |
|  | 35B | 0(0) | 1(20) | 0(0) | 1(9) |
|  | 35F | 1(25) | 0(0) | 0(0) | 1(9) |
| **Case fatality** |  |  |  |  |  |
|  |  | 0(0) | 2(67) | 1(50) | 3(27) |

**Key**

**PCV13 = Serotypes included in 13 valent Pneumococcal Conjugate Vaccine**

**Non-PCV13= Serotypes NOT included in 13 valent Pneumococcal Conjugate Vaccine**