**RISK OF INVASIVE PNEUMOCOCCAL DISEASE IN CHILDREN WITH SICKLE CELL DISEASE IN THE ERA OF CONJUGATE VACCINES: A systematic review of the literature.**

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**Abstract**

Pneumococcal conjugate vaccines (PCVs) are highly effective in preventing invasive pneumococcal diseases (IPD) in children, including those with sickle cell disease (SCD). A systematic review of the English literature published from 2000 to 2017 was undertaken to evaluate the serotype distribution, clinical presentation and outcomes of IPD in children with SCD in PCV programmes.

We identified 475 potential studies and included 16 publications involving 9,438 children up to 22 years of age with SCD and 182 IPD episodes (prevalence, 1.9%. 95% CI, 1.7-2.2%). Septicaemia was the most prevalent clinical presentation (84/137; 61%) followed by lower respiratory tract infection (39/137; 29%) and meningitis (12/137, 9%). More than half the serotypes associated with IPD (88/148; 59.5%) were not included in the 13-valent PCV; of these, 54% (44/82) were due to serogroup 15. The crude case fatality rate was 11.5% (21/182 cases; 95% CI, 7.3-17.1%). Most cases of IPD in children with SCD were due to serotypes that are not included in any of the licensed PCVs. IPD in children with SCD remains associated with high morbidity and mortality, highlighting the importance of strict adherence to daily penicillin prophylaxis. Until a serotype-independent pneumococcal vaccine becomes available, higher-valent PCVs should include serogroup 15 to protect this highly vulnerable group of children

**Key words**: invasive pneumococcal disease; pneumococcal conjugate vaccines; sickle cell disease; serotypes; fatality

**Introduction**

Sickle cell disease (SCD) is an important cause of childhood morbidity and mortality worldwide (Stuart & Nagel, 2004). Such children often have functional asplenia, with dysfunctional antibody production and poor opsonophagocytosis, making them susceptible to serious and potentially lethal infections by encapsulated bacteria, especially *Streptococcus pneumoniae* (Beauvais, 1982; Pearson, 1977; Battersby *et al*, 2010). In the absence of any intervention, children with SCD have a 600-fold higher risk of invasive pneumococcal disease (IPD) compared to healthy children without SCD (Overturf *et al*, 1977). With penicillin prophylaxis and 23-valent pneumococcal polysaccharide vaccination (PPV23), this risk is reduced substantially, although children with SCD continue to have a 10-100-fold higher risk of IPD, with reported case fatality rates of up to 15% in industrialised countries (Adamkiewicz *et al*, 2003; Hord *et al*, 2002; Gaston *et al*, 1986).

In 2000, the 7-valent pneumococcal conjugate vaccine (PCV7) was licensed to protect against the seven most prevalent pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) causing IPD in children. In 2010-2011, PCV7 was replaced with a 13-valent vaccine (PCV13) in most industrialised countries that aimed to protect against six additional serotypes (1, 3, 5, 6A, 7F, and 19A). Another licensed PCV formulation, PCV10 that protects against serotypes 1, 5, and 7F in addition to PCV7 serotypes was also licensed at around the same time and implemented in other countries. All three vaccines have led to rapid and sustained declines in IPD caused by the respective vaccine serotypes, in both healthy children and in those with comorbidities such as SCD (Conklin *et al*, 2014; Davies *et al*, 2004; Black *et al*, 2000). Most childhood IPD cases are now due to non-PCV serotypes; recent reports have identified differences in infecting serotypes and clinical presentation among children with SCD who develop IPD, as well as a shift in case fatality to older age groups (Martin *et al*, 2018).

The implication of these findings has not been systematically assessed in children with SCD. We, therefore, conducted a systematic review of published studies to evaluate the risk factors, clinical presentation, serotype distribution and outcomes of IPD in children with SCD following the introduction of PCVs. It is hoped that the findings of this systematic review will provide more robust evidence to improve the prevention of IPD in children with SCD.

**Methods**

**Search strategy**

A search strategy was designed to identify observational studies (cohort study, case-control study, case series) reporting IPD in children with SCD aged less than 22 years old in the era of pneumococcal conjugate vaccines. We searched MEDLINE, EMBASE, and the Cochrane library from 01 January 2000 to 30 December 2017. We also searched the papers using the ISI web of knowledge, to identify relevant articles and conference proceedings. The medical subject headings (MeSH) terms used included ‘‘pneumococcal conjugate vaccines”, ‘‘sickle cell disease”, ‘‘Heamoglobinopathy”, “HbSS”, “HbSC”, ‘‘invasive pneumococcal disease”, ‘‘Streptococcus pneumoniae”, ‘‘pneumococcus”, ‘‘pneumococcal infection”, ‘‘child”, ‘‘infant”, ‘‘toddler”, “adolescence”, ‘‘PCV7, ‘‘PCV13”, ‘‘PCV9”, ‘‘PCV10”, and ‘‘risk factors”. The full search strategies are shown in Appendix 1. We only included studies published in English language in our review. In addition, we screened reference lists of selected papers to retrieve relevant studies.

**Study selection**

Studies were eligible for inclusion if they reported IPD in children with SCD from observational studies and surveillance databases. IPD was defined as *S. pneumoniae* cultured from a normally sterile site or pneumococcal DNA detected in cerebrospinal fluid (CSF) or pleural fluid. Comorbidity was defined as presence of a high-risk condition as determined by the reporters. Studies were excluded if they were case reports, laboratory or experimental studies, or not original research. Two independent reviewers (G.O. and S.L.) screened the title and abstract of papers identified by the electronic searches, evaluating inclusion and exclusion criteria for all papers. Full articles of included publications were retrieved and each publication was independently reviewed for eligibility. Discrepancies were resolved by discussion with a third author (M.F.).

**Quality assessment and data extraction**

Two reviewers (G.O. and S.L.) independently reviewed the methodological quality of included studies, comparability of case and controls, and outcomes. The explanatory variables extracted included: study design, country, description of study subjects, sickle genotype, pneumococcal vaccine era, serotype, underlying co-morbidity, clinical presentation and outcome of infection. The study quality assessment was undertaken according to the Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for the conduct and reporting of systematic reviews (Moher *et al*, 2010).

**Data analysis**

Included studies are summarised using descriptive analyses to provide an overview of the information on IPD, haemoglobinopathy, reported clinical presentations, underlying co-morbidity, serotype distribution, and IPD outcomes. Where possible, we extracted the number of IPD cases within each study to calculate the prevalence of IPD in children with SCD. We calculated the percentage with exact binomial 95% confidence interval (CI) for the outcome of interest where data were available.

**Results**

**Study characteristics**

We identified 475 potential studies, of which 66 were duplicates. A further 299 were excluded on the basis of title and abstracts, with another 96 studies not meeting the eligibility criteria on full-text review of the articles. One French study (Couque *et al*, 2016) identified IPD deaths in children with SCD following the assessment of medical care in their cohort of newborns with SCD with no report on number of IPD cases or period of death (i.e. pre- or post-PCV era); this study was excluded. The remaining 16 studies were included in the final analysis (Narang *et al*, 2012; Navalkele *et al*, 2017; Patel *et al*, 2013; Payne *et al*, 2013; Rogovik *et al*, 2010; Soothill *et al*, 2016; Adamkiewicz *et al*, 2008; Baskin *et al*, 2013; Brown *et al*, 2017; Halasa *et al*, 2007; McCavit *et al*, 2011; Shihabuddin & Scarfi, 2014; Chang *et al*, 2013; Oligbu *et al*, 2017; Ellison *et al*, 2013; Martin *et al*, 2018). We found large variations in study methodology and quality. Most studies included children but the age range varied widely. One study included adults up to the 44 years (Halasa *et al*, 2007), but we were able to extract data for <15 year-olds. In one other US study, the prevalence of SCD was estimated from the supplemental digital content 1, <http://links.lww.com/INF/B629> (Payne *et al*, 2013). Most reports involved PCV7 only (62.5%; 10/16), two PCV13 (12.5%; 2/16), and four involved both PCV7 and PCV13 (25%; 4/16). There were no studies reporting PCV10 use in children with SCD and IPD. Most studies reported IPD cases in <18 years-old (31%, n=5/16) or <21 years-old (25%, n=4/16). Two studies assessed patients aged <5 years (13%, n=2), and one each for <15 years (including one which had this data extracted from data for all ages), <10 years, <16 years, <17 years and <22 years (6%, n=1).

Of the included studies, IPD cases in children with SCD were identified through regional surveillance and/or hospital records. **Tables 1 and 2** summarise the study design, data collection method, study subjects, and clinical presentation. Most studies were from the United States (75%, n=12/16), followed by two studies from Africa (13%, n=2), and one study each from Canada (6%, n=1) and Europe (6%, n=1). Three studies reported detailed co-morbidities among IPD cases (Martin *et al*, 2018; Narang *et al*, 2012; Oligbu *et al*, 2017) while two studies reported presence of central venous lines (CVL) as a possible contributing factor for IPD (Chang *et al*, 2013; Ellison *et al*, 2013)

Most reports included information on penicillin prophylaxis, although adherence was not formally assessed, and all studies reported introduction of a PCV programme except the study from Nigeria, where vaccination uptake was reported to be poor (Brown *et al*, 2017). In studies that reported vaccination status, the proportion of IPD cases that were vaccinated with PCV varied significantly from 0% to 80% **(*Table 1*).**

A total of 9,438 participants aged up to 22 years with SCD were included in the final analysis and 182 developed IPD **(Table 1)**, giving a crude prevalence of 1.9% (95% CI, 1.7-2.2%). The median age was 4.8 years and 58% (n=49/85) were male. Eleven studies reported haemoglobin genotype; 79% (n=79/100) were homozygotes for haemoglobin S (HbSS), 17% (n=17) compound heterozygote for haemoglobin S and C (HbSC), 3% (n=3) compound heterozygote for haemoglobin S and B+ thalassemia (HbSB+) and 1% (n=1) compound heterozygote for HbS and O-Arab (HbSO). Among the twelve studies reporting clinical presentation, septicaemia was the commonest (n=84/137; 61%) followed by lower respiratory tract infection (n=39/137; 29%), meningitis (n=12/137, 9%), arthritis (n=1; 1%) and, in one case (1%), the clinical presentation was not reported.

Of the 11 studies reporting serotypes responsible for IPD, non-PCV13 serotypes predominated (n=88/148; 60%), followed by PCV7 (n=37, 25%) and PCV13 (n=23, 16%). The 20 vaccine-serotype IPD cases were due to serotype 23F (n=4), 6A (n=4), 7F (n=3), 19A (n=3), 19F (n=2), 14 (n=2), and 6B (n=2). Of the non-PCV13 serotypes, half was due to serogroup 15 (A/B/C; n=44/82; 54%) (**Table 3**). Only 13 studies reported patient outcome, with a crude case fatality rate (CFR) of 11.5% (21/182 cases; 95% CI, 7.3-17.1%) and a median age at death of 2.0 years. Among the 21 fatalities, seven serotypes were included: 15A/B/C (57%, n=4/7), 23F (28.6%, n=2/7) and 23A (14.7%, n=1/7). Clinical presentation was reported for five of the fatalities; septicaemia in four and pneumonia in one case.

**Discussion**

A thorough systematic review of the literature identified a very low rate of IPD in children with SCD in the era of pneumococcal conjugate vaccines. IPD was reported in 1.9% of children with SCD overall, many of whom also had other associated comorbidities. More than half the serotypes causing IPD in children with SCD were due to non-PCV13 serotypes and, of these, serogroup 15 was responsible for half the cases. Septicaemia was the most common clinical presentation, followed by lower respiratory tract infection and meningitis. The crude case-fatality rate was 11.5%.

Several studies have reported substantially lower IPD rates in children with SCD during the PCV period when compared to the PPV23 era (Oligbu *et al*, 2017; Payne *et al*, 2013; McCavit *et al*, 2012). Children with SCD, however, continue to remain at higher risk of IPD compared to their healthy peers without SCD. The majority of pneumococcal infections in countries with established PCV programmes are due to non-PCV serotypes.

A consistent finding was that, after PCV7 introduction and subsequent replacement with PCV13, serogroup 15 appears to be a particularly common cause of IPD among children with SCD, accounting for half of IPD cases in this review. 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 (Carter *et al*, 2014). However, the virulence and aggressiveness of this serogroup compared to other more prevalent serotypes is not known and additional studies are needed to better understand this observed association.

The overall CFR in the published studies was 11.5%, which, although lower than the 15% reported in industrialised countries prior to PCV introduction (Adamkiewicz *et al*, 2003; Hord *et al*, 2002; Gaston *et al*, 1986), remains unacceptably high. In many countries, PPV23 is recommended for at-risk individuals from 2 years of age, including SCD. This vaccine aims to protect against 11 additional serotypes, including 15B, which is a frequent cause of IPD in patients with SCD. Unlike PCVs, however, PPV23 is a polysaccharide vaccine and therefore, only activates a B-cell immune response leading to a predominantly IgM response without an immunological memory response, as well as rapid waning of protection compared to polysaccharide-conjugate vaccines. The effectiveness of PPV23 in children, especially those at risk of IPD, remains controversial (Borrow *et al*, 2012). Until a conjugate vaccine containing the additional PPV23 serotypes becomes available, any protection afforded by this vaccine, even if short-term, is likely to be beneficial in this highly vulnerable group who appear to be particularly susceptible to some of the additional PPV23 serotypes.

Most importantly, however, the results of this systematic review highlight the need to continually educate and advise parents on the need for strict adherence to penicillin prophylaxis, which will not only help protect against all pneumococcal infections – irrespective of serotype, but also against other encapsulated bacteria (Berkovitch *et al*, 1998). This is particularly important in African countries where the prevalence of SCD and infectious diseases are both very high. A recent review, for example, estimated that African people with SCD not only had a 36-fold higher odds of IPD, but also a 13-fold higher odds of *Haemophilus influenzae* type b (Hib) disease and a 19-fold higher odds of developing other invasive bacterial infections compared to controls (Ramakrishnan *et al*, 2010).

In addition, in a systematic review looking at the effect of prophylactic antibiotics in children with SCD, it was concluded that prophylactic penicillin significantly reduces risk of pneumococcal infection in children with SCD but no conclusive evidence on the appropriate age for withdrawal (Rankine-Mullings & Owusu-Ofori, 2017). Therefore, until further evidence emerges, children will continue to benefit from daily oral prophylactic penicillin as a preventative measure till the age of 5 (Yawn *et al*, 2014).

Our results demonstrate the potential strengths of combining outcomes of rare events through a systematic review of the literature. However, several potential biases might limit the interpretation of our findings and contribute to the heterogeneity of the results. The studies did not assess compliance or adherence with penicillin prophylaxis and, where information on penicillin prophylaxis was provided, we were unable to compare patients who received penicillin prophylaxis with those who didn’t either because of a lack of reporting of non-compliance or because the age at which penicillin prophylaxis was stopped varied. Information on vaccination status of cases was also poor. We were also unable to compare differences in haemoglobin genotype or calculate risks associated with clinical outcomes because of differences in definition of the sickle cohort included in the different studies.

**Conclusions**

Children with SCD remain at increased risk of IPD despite all current interventions, including recommendations for daily penicillin prophylaxis and timely immunisation with highly effective conjugate vaccines. Given that most serotypes causing IPD in children with SCD are now no longer preventable by the current conjugate vaccines, we must continue to increase efforts to improve uptake and adherence to penicillin prophylaxis. Further studies should assess the impact of emerging serotypes causing IPD in children with and without SCD. Our findings also highlight the need for a conjugate vaccine that can protect serogroup 15 or, preferably, a universal vaccine targeting all pneumococci irrespective of their capsular serotype (Ladhani & Ramsay, 2015).

## **Footnotes**

These data were presented at the recently concluded Royal College of Paediatrics and Child Health Conference 2018, and the abstract has been published in BMJ as cited below: Oligbu G, Pay L, Fallaha M*, et al.* **Risk of invasive pneumococcal disease in children with sickle cell disease in the era of conjugate vaccines: a systematic review of the literature.** *Archives of Disease in Childhood*2018;**103:**A150.

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**Authors’ contributions**

GO conceptualised and designed the study, reviewed the literature, analysed the data, was involved in the interpretation of the data and writing the report (including the first draft), co-ordinated the production of the manuscript, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, and approved the final manuscript as submitted. MF and LP carried out the initial analyses, were involved in the interpretation of the data and writing the report, and approved the final manuscript as submitted. SL reviewed the literature, was involved in the interpretation of the data and writing the report, co-ordinated the production of the manuscript, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

**Potential conflicts of interest**

S.L. have provided vaccine manufactures with postmarketing surveillance reports which the companies are required to submit to the UK Licensing authority in compliance with their risk management strategy. In accordance with Public Health England (PHE) policy, a cost recovery charge is made for these reports payable to the Immunisation Department. S.L. performs contract research on behalf of PHE for GSK, Novartis, Pfizer, and Sanofi Pasteur. All other authors report no potential conflicts.

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**Fig. 1. Identification and selection of eligible studies in the systematic review**.

Additional records identified through other sources  
(n =3)

Records identified through database searching  
(n = 472)

Records after duplicates removed  
(n = 409)

Did not meet eligibility criteria after full text screening  
(n = 85)

Studies eligible for inclusion   
(n =25)

Further exclusion due to incomplete & duplicate data)  
(n = 9)

Studies included in qualitative synthesis  
(n = 16)

**Table 1: Description of study designs and reported Invasive Pneumococcal Disease in children with Sickle Cell Disease**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Publication Year** | **Country** | **Study Design** | **Study years** | **Duration of observation (yr)** | **Age** | **PCV** | **Study participant** | **IPD cases** | **IPD cases as % of study participants** | **SCD Type** | **Ethnicity** | **Penicillin Prophylaxis** | **Conjugate Vaccination status (in IPD patients)** |
|  |  | **UNITED STATES** | | | | | | | | | | | | |
| **McCavit** (McCavit *et al*, 2011) | 2011 | US (Texas) | Case series | 2000-2009 | 9.0 | 0-16yr | PCV7 + PPV23 | 650 | 10 | 1.5 | HbSS:8 HbSC:1  HbSB:1 | Not reported | 7 (70%) | Vaccinated: 8 (80%), of which:  PCV7: 4(50%)  PCV7+PPV23: 4 (50%) |
| **Shihabuddin BS** (Shihabuddin & Scarfi, 2014) | 2014 | US (NJ) | Case series | 2001-2011 | 10.5 | 2m – 18yr | PCV7 | 307 | 1 | 0.3 | HbSS:1 | Not reported | Not reported | Not reported |
| **Narang** (Narang *et al*, 2012) | 2012 | US (NY) | Retrospective cohort | 1997-2006 | 9.5 | <18yr | PCV7 | 120 | 1 | 0.8 | HbSC:1 | Not reported | Yes (+ anti-retroviral) | Not reported |
| **Patel** (Patel *et al*, 2013) | 2013 | US (Alabama) | Retrospective cohort | 2006-2012 | 6.5 | 2m – 18yr | PCV7 + PCV13 | 134 | 2 | 1.5 | HbSS:2 | Not reported | Yes | Complete: 1(50%), Incomplete: 1(50%) |
| **Payne** (Payne *et al*, 2013) | 2013 | US (ABCs) | Retrospective cohort | 1998-2009 | 11.0 | <18yr | PCV7 | 2688 | 96 | 3.6 | HbSS: NA HbSC: NA | African-American | Not reported | Not reported |
| **Martin O** (Martin *et al*, 2018) | 2017 | US (Minnesota) | Retrospective cohort | 2000-2014 | 14.0 | 0-21yr | PCV7 + PCV13 | 380 | 11 | 2.9 | HbSS:9, HbSC;1  HbSB:1 | Not reported | Yes | Vaccinated: 8 (72.7%), Unknown: 3(27.2%) |
| **Navalkele** (Navalkele *et al*, 2017) | 2017 | US (Michigan) | Retrospective cohort | 2004-2013 | 10.0 | 0-21yr | PCV7 + PCV13 | 242 | 8 | 3.3 | HbSS:7  HBS0 Arab:1 | African-American | Yes | 7 (87.5%) |
| **Adamkiewics** (Adamkiewicz *et al*, 2008) | 2008 | US (Georgia) | Retrospective cohort | 1995-2003 | 8.0 | 0-10yr | PCV7 | 1247 | 14 | 1.1 | HbSS:12 HbSC:2 | Not reported | Not reported | 4 (28.6%) |
| **Baskin** (Baskin *et al*, 2013) | 2013 | US (Boston) | Retrospective cohort | 1993-2010 | 18.0 | <21yr | PCV7 | 627 | 2 | 0.3 | HbSS:2 | Not reported | Not reported | Complete: 1(50%)  Incomplete: 1(50%) |
| **Chang** (Chang *et al*, 2013) | 2013 | US (Los Angeles) | Retrospective cohort | 1993-2009 | 17.0 | 0-21yr | PCV7 | 466 | 5 | 1.1 | HbSS:5 | Not reported | Not reported  Cohort compliance:47.3% | Not reported |
| **Ellison** (Ellison *et al*, 2013) | 2013 | US (Philadelphia) | Retrospective cohort | 2000-2010 | 11.0 | 2m – 22yr | PCV7 | 815 | 12 | 1.5 | HbSS:9  HbSC:2  HbSB+:1 | Not reported | Not reported | Not reported |
| **Halasa** (Halasa *et al*, 2007) | 2007 | US (Tennessee) | Retrospective cohort | 1995-2004 | 10.0 | 0-5yr | PCV7 | 268 | 6 | 2.2 | Not reported | African | Not reported | Vaccinated: 0 (0%) |
|  |  | **CANADA** | | | | | | | | | | | | |
| **Rogovik** (Rogovik *et al*, 2010) | 2010 | Canada | Case series | 2005-2006 | 2.0 | 0-18 | PCV7 | 248 | 0 | 0 | None | Not reported | N/A | N/A |
|  |  | **EUROPE** | | | | | | | | | | | | |
| **Oligbu** (Oligbu *et al*, 2017) | 2017 | UK | Prospective cohort | 2010-2015 | 5.3 | <5 | PCV13 | 1004 | 12 | 1.2 | HbSS:11  HbSC:1 | African:7 Carribean:2 Mixed:2  Unknown:1 | Yes  (compliance not assessed) | Vaccinated: PCV13+PPV23 |
|  |  | **AFRICA** | | | | | | | | | | | | |
| **Soothill** (Soothill *et al*, 2016) | 2016 | The Gambia | Case series | 2010-2015 | 5.0 | 0-15 (extracted) | PCV7 +PCV13 | 126 | 1 | 0.8 | Not reported | African | No | Not reported |
| **Brown** (Brown *et al*, 2017) | 2017 | Nigeria | Cross-sectional | 2013-2014 | 1.3 | 0-17 | PCV13 | 116 | 1 | 0.9 | HbSS:1 | African | Not reported | Unvaccinated |

**Abbreviations:** IPD; invasive pneumococcal disease; m: month; yr: year; NA: Not available; PCV: Pneumococcal Conjugate Vaccines, SCD; Sickle Cell Disease; ABCs, Active Bacterial Core Surveillance; US, United States; UK, United Kingdom.; HbSS, homozygotes for haemoglobin S; HbSC, heterozygotes for haemoglobin S and C

**Table 2: Characteristics of children with SCD who developed IPD in the published studies that were included in the systematic review**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Publication Year** | **Country** | **Median Age at diagnosis (yr)** | **Clinical Presentation** | **Serotype Isolated** | **Deaths (n)** | **CFR (%)** | **Age at Death (yr)** | **Serotype isolated in death cases** | **Co-morbidities** |
| **McCavit** (McCavit *et al*, 2011) | 2011 | US (Texas) | 2 | Septicaemia: 5,  LRTI: 2,  Meningitis: 1,  Septic arthritis: 1, Unknown: 1. | 15A/C/F: 1  19A: 2  7B/C: 1  23A: 3  23B: 1  6A: 1  Unknown: 1 | 1 | 10 | 6 | 23A | None |
| **Shihabuddin BS** (Shihabuddin & Scarfi, 2014) | 2014 | US (NJ) | 4 | Bacteremia: 1 | Not reported | 0 | 0 | - |  | None |
| **Narang** (Narang *et al*, 2012) | 2012 | USA (NY) | 7 | Bacteraemia: 1 | Not reported | 0 | 0 | - |  | Perinatal HIV infection |
| **Oligbu** (Oligbu *et al*, 2017) | 2017 | UK | 1.1 | Septicaemia: 8  Pneumonia: 4 | 7F: 1  15: 1  15A: 2  15B: 5  35B: 1  35F: 1  33F: 1 | 3 | 25 | 1,  1, &  2 | 15B/C | Prematurity: 2 |
| **Patel** (Patel *et al*, 2013) | 2013 | US (Alabama) | 5 | Bacteraemia: 2 | 23B: 1  23F: 1 | - | 0 | - | - | None |
| **Payne** (Payne *et al*, 2013) | 2013 | US (ABCs) | 4.8 | Meningitis: 10  LRTI: 29,  Septicaemia: 57 | NVT: 44 {6C:13  15A:9,  15B/C:12,  15A:5, NA:5}  PCV13: 13 PCV7: 27. | 12 | 12.5 | Not reported | - | None |
| **Rogovik** (Rogovik *et al*, 2010) | 2010 | Canada | 0 | None | None | 0 | 0 | - | - | None |
| **Soothill** (Soothill *et al*, 2016) | 2016 | The Gambia | Not reported | Meningitis: 1 | Not reported | 0 | 0 | - | - | Not reported |
| **Martin O** (Martin *et al*, 2018) | 2017 | US (Minnesota) | 5 | Not reported | 15C: 1  23B: 1  37: 1  19A: 1  23A: 1  16F: 1  34: 1  6A: 1  7F: 1  Unknown: 2 | 2 | 18.2 | 2,  8 | Not reported | Splenectomy: 1 |
| **Navalkele** (Navalkele *et al*, 2017) | 2017 | US (Michigan) | 5 | Bacteremia: 7  LRTI: 1 | 15A/C: 3  Others: NA | 1 | 12.5 | 5 | 15A | None |
| **Adamkiewics** (Adamkiewicz *et al*, 2008) | 2008 | US (Georgia) | **2.9** | Not reported | 6B: 2  14: 4  10A: 1  19F: 1  33F: 1  23F: 3  Unknown: 2 | Not reported | Not reported | Not reported | - | None |
| **Baskin** (Baskin *et al*, 2013) | 2013 | US (Boston) | 10 | Septicaemia: 2 | 15A: 1  15C: 1 | 0 | 0 | - | - | None |
| **Brown** (Brown *et al*, 2017) | 2017 | Nigeria | 6 | Septicaemia: 1 | Not reported | 0 | 0 | 0 | - | None |
| **Chang** (Chang *et al*, 2013) | 2013 | US (Los Angeles) | 6 | Not reported | Not reported | 0 | 0 | - | - | CVL |
| **Ellison** (Ellison *et al*, 2013) | 2013 | US (Philadelphia) | 7.1 | ACS+LRTI: 3 | 6A: 2  7F: 1  8: 1  19F: 1  23B: 4  23E: 2  29: 1 | Not reported | Not reported | Not reported | - | CVL |
| **Halasa** (Halasa *et al*, 2007) | 2007 | US (Tennessee) | Not reported | Not reported | 12F: 1  35B: 1  15C: 1  Others: NA | 2 | 33 | 1.4, &14.7 | 23F: 2 | None |

.

**Abbreviations:** PCV: pneumococcal conjugate vaccine; PCV7: 7-valent pneumococcal conjugate vaccine; PCV13; 13-valent pneumococcal conjugate vaccine; LRTI: Lower respiratory tract infection; ACS: Acute Chest Syndrome; NVT: Non-vaccine-type IPD; m: month; n; number; yr: year; SCD; Sickle Cell Disease; ABCs: Active Bacterial Core Surveillance; CVL: Central Venous Line; NA, Not Available; US, United State; UK: United Kingdom

|  |  |  |
| --- | --- | --- |
| **Table 3: Serotypes isolated in IPD cases** |  |  |
|  |  |  |
| **PCV** | **Serotypes** | **Number** |
| **PCV7** | 23F | 4 |
|  | 6B | 2 |
|  | 14 | 2 |
|  | 19F | 2 |
| **PCV13** |  |  |
|  | 7F | 3 |
|  | 19A | 3 |
|  | 6A | 4 |
| **Non-PCV13** |  |  |
|  | 15 | 1 |
|  | 15A | 17 |
|  | 15B | 5 |
|  | 15C | 6 |
|  | 15B/C | 12 |
|  | 15A/C | 3 |
|  | 35B | 2 |
|  | 35F | 1 |
|  | 23B | 7 |
|  | 23A | 4 |
|  | 23E | 2 |
|  | 6C | 13 |
|  | 37 | 1 |
|  | 16F | 1 |
|  | 34 | 1 |
|  | 10A | 1 |
|  | 33F | 1 |
|  | 8 | 1 |
|  | 29 | 1 |
|  | 12F | 1 |
|  | 7B/C | 1 |
|  |  |  |

**Abbreviations**: PCV: pneumococcal conjugate vaccine; PCV7: 7-valent pneumococcal conjugate vaccine; PCV13; 13-valent pneumococcal conjugate vaccine; Non-PCV13; Non 13-valent pneumococcal conjugate vaccine; IPD: invasive pneumococcal disease

**Appendix 1**

Database: Medline

Search for: limit [11] to (English language and yr=”2000 – Current)

Search strategy:

--------------------------------------------------------------------------------------------

1 Anemia, Sickle Cell [Mesh]

2 “sickle”

3 “SCD”

4 [1] OR [2] OR [3]

5 Pneumococcal Vaccines [Mesh]

6 “PCV” OR ‘’PCV7” OR “PCV13” OR “PCV10”

7 “pneumococcal conjugate vaccine\*”

8 “streptococcus pneumoniae\*”

9 “invasive pneumococcal disease\*”

10 [5] OR [6] OR [7] OR [8] OR [9]

11 [4] AND [10]

Database: Embase

Search for: limit [12] to (English language and yr=”2000 – Current)

Search strategy:

--------------------------------------------------------------------------------------------

1 Sickle cell [Mesh]

2 sickle cell anemia [Mesh]

3 sickle cell trait [Mesh]

4 hemoglobin SC disease [Mesh]

5 hemoglobin SD disease [Mesh]

6 sickle cell beta thalassemia [Mesh]

7 “sickle cell trait”

8 “SCD”

9 [1] OR [2] OR [3] OR [4] OR [5] OR [6] OR [7] OR [8]

10 pneumococcus vaccine [Mesh]

11 invasive pneumococcal disease [Mesh]

12 [9] AND [10] AND [11]