Pneumococcal Infections in Children with Sickle Cell Disease Before and After Pneumococcal Conjugate Vaccines.

Supplement material

Pneumococcal vaccines:

- PCV7 (Wyeth Pharmaceutical): serotypes 4, 6B, 9V, 14, 18C, 19F and 23F
- PCV9 (Wyeth Pharmaceutical): PCV7 plus serotypes 1 and 5
- PCV10 (GlaxoSmithKline, Serum Institute of India): PCV9 plus serotypes 7F
- PCV11 (Sanofi Pasteur): PCV10 plus serotype 3
- PCV13 (Wyeth Pharmaceutical/Pfizer): PCV11 serotypes plus 6A and 19A
- PCV15 (Merck Sharp & Dohme): PCV13 serotypes plus 22F and 33F
- PCV20 (Wyeth Pharmaceutical/Pfizer): PCV15 serotypes plus 8, 10A, 11A, 12F and 15B
- PCV21 (Sanofi-Pasteur, in development): PCV20 plus 9N
- PCV21 (Merck Sharp & Dohme, in development, V116):
    - Serotypes in PCV20 and PCV21: 3, 6A*, 7F, 8, 10A, 11A, 12F, 15B*, 19A, 22F, 33F
    - Serotypes not PCV20 : 9N, 15A, 16F, 17F, 20, 23A, 23B, 24F, 31, 35B
    - *plus immune response against 6C, 15C.
- PPSV23 (Pneumovax23, Merck Sharp & Dohme)
    - PCV20 serotypes, plus 2, 9N, 17F and 20; minus 6A
    - PCV21 serotypes, plus 1, 2, 4, 5, 6B, 14, 18C, 19F, 23F, minus: 6A, 15A, 16F, 23B, 24F, 31, 35B
- For examples of other pneumococcal vaccines in development, see reference.[70]

(PCV: polysaccharide capsule conjugated to protein; PPSV: polysaccharide capsule)

Study population:

Before 1997, the initial 8 counties[23] GA-EIP catchment area included Clayton, Cobb, DeKalb, Douglas , Fulton , Gwinnett, Newton, and Rockdale counties. The additional 12 peripheral counties added in 1997 onward[23] included (Barrow, Bartow, Carroll, Cherokee, Coweta, Fayette, Forsyth, Henry, Paulding, Pickens, Spalding, and Walton counties.[23]

Population of children with SCD:

Data from both databases (1994-2002 and 2003-2018), were matched to hospital administrative electronic data to ensure that all encounters at CHOA for all patients with SCD were included in the analysis, whether or not a SCD ICD code was associated with the encounter.[17] Both SCD databases were also matched to the GA-EIP IPD database, using variables that included acrostic (first three letters of the last name and first two letters of the first name), date of birth, sex, last four digits of medical record number, and co-morbidity diagnoses in the GA-EIP IPD database (from 1/1/1994 until 7/31/2018). Clinical features of IPD cases identified by the GA-EIP, and/or by additional chart review[13,17] included history of oral penicillin prophylaxis, hydroxyurea administration, surgical splenectomy, bone marrow transplantation, meningitis and mortality.

Compared to the previous match,[17] 6 additional IPD were identified. Six cases of meningitis (including one in a child with HbSC) were identified by chart review separate from the GA-EIP prior to 2002.[17] Also one patient that died with an unknow serotype in GA-EIP, was typed separately at the CDC as part of the prior surveillance (19F),[13] and another child died from IPD was not identified as such in in the GAEIP. These were included in the analysis. One previously identified IPD not identified in the current match, was only included in vaccine effect analysis (serotype 10A).

Pooled data:

the pooled data, IPD serotype in children with SCD was retrieved from 12,[13,40,49,7150,72-78] out of 216 (6%) studies containing search terms. Additional surveillance case-reports from outside of Atlanta were included.[13,40] Fourteen IPD episodes in two studies were excluded because only isolate serogroup was reported or serotype was incompletely characterized.[71,73] In the pooled data, 26% (46/177) of IPD episodes were with non-PCV13 serotypes: 36;[71] 15B, 18B, 18F;[49] 9N, 12F, 15B, 15C: 2, 18F, 23A, 23B;[13] 22F, 23B (data from TVA);[40] 12F, 15C, 35B;[50] 13, 18F, 23B;[72] 23A: 3, 23B;[73] 15A, 15C;[74] 23B;[75] 15A, 15C: 2;[76] 15C, 16F, 23A, 23B, 34, 37;[77] 15A: 2, 15BC: 5, 35B, 35F;[78] meningitis: 15C, meningitis/death: 18F;[13] death: 13A [73] death: 15A;[76] death: 15BC, 3.[78] IPD typed as 7BC or 15ACF were excluded.[73] Children with IPD were from the USA: 32 (70%);[13,40,49,50,73-77] UK: 10 (22%);[78] Kenya: 3 (7%);[72] Jamaica: 1 (2%);[71] and included HbSS: 23 (50%); HbSC: 22(49%); HbSbeta thalassemia 0: 1 (2%); IPD in children with SCD from the current study were excluded from the pooled data. Non-PCV13 serotypes distribution of pooled data was not significantly different from the present study (p=0.1912). Because of limited data on IPD serotype in children with SCD in Africa, a study of pneumococcal nasopharyngeal carriage in patients with SCD from Ghana after introduction of pneumococcal conjugate vaccines (PCV10, PCV13) was examined.[41] Serotype was characterized in 94% (67/71) of samples, 60% (40) of which were non-PCV13 serotypes.[41] Non-PCV13 nasopharyngeal carriage in patients from

Ghana serotype distribution was significantly different from IPD serotype distribution in Atlanta or in the pooled IPD data, $p<0.0001$.

Note for Table 5: Before 2000 IPD in children were significantly more likely to be resistant to penicillin compared to the reference population but not after 2009. Changes in adherence to penicillin prophylaxis may explain this trend.[12]

Table 5: IPD Minimal inhibitory concentration (MIC) to penicillin frequencies in children with SCD (HbSS/SC) ages 0-9 years compared to reference population, with relative risk (RR).

MIC	Pre-PCV period 1994 - 1999			PCV7 period 2000 - 2009			PCV13 period 2010 - 2018		
µg/mL	Reference	HbSS/SC	RR (95 % CI), p	Reference	HbSS/SC	RR (95 % CI), p	Reference	HbSS/SC	RR (95 % CI), p
<=0.06	513 (60.8%)	18 (41.9%)	0.7 (0.5,1.0), 0.016	284 (55.30%)	14 (41.20%)	0.7 (0.5,1.1), 0.154	89 (51.70%)	9 (52.90%)	1.0 (0.6,1.6), 1.000
0.12-1	181 (21.4%)	11 (25.6%)	1.2 (0.7,2.0), 0.568	97 (18.90%)	11 (32.40%)	1.7 (1.0,2.9), 0.073	39 (22.70%)	6 (35.30%)	1.6 (0.8,3.1), 0.244
>=2	150 (18%)	14 (32.6%)	1.8 (1.2,2.9), 0.024	133 (26%)	9 (26.50%)	1.0 (0.6,1.8), 1.000	44 (26%)	2 (11.80%)	0.5 (0.1,1.7), 0.252
Total	844 (100%)	43 (100%)		514 (100%)	34 (100%)		172 (100%)	17 (100%)	

IPD: invasive pneumococcal infection MIC: minimal inhibitory concentration; Hb: hemoglobin; RR: relative risk; CI: confidence interval.

Note for Table 6: Indirect-cohort effect analysis, when indicated, analysis assumed that PPSV23 not affective after three years.[45]

Table 6. Indirect-cohort effect* of PPSV23 vaccination on non-PCV13 PPSV23 related isolates (including 15A, 15C) in children with SCD with sensitivity analysis.

Analysis	Age (years)	IPD occurrence after PPSV23	Not vaccinated, n (%)		Vaccinated, n (%)		Effect (95 % CI), p value	
			Total	Serotype covered in PPSV23	Total	Serotype covered in PPSV23	Unadjusted	Adjusted
Main effect	**0-9**	**< 3 years**	21	17 (81.0%)	13	5 (38.5%)	85.3 (30.0,96.9), 0.025	92.4 (40.8,99.0), 0.014
Sensitivity analysis		**Any time**	17	14 (82.4%)	17	8 (47.1%)	81.0 (8.5,96.0), 0.071	89.6 (-3.4,98.9), 0.053
	2-9	**< 3 years**	14	12 (85.7%)	13	5 (38.5%)	89.6 (32.6,98.4), 0.018	93.8 (37.8,99.4), 0.018
		Any time	10	9 (90.0%)	17	8 (47.1%)	90.1 (3.9,99.0), 0.042	89.6 (-3.5,99.0), 0.053

CI: confidence interval; analysis includes HbSS and HbSC; See further details in supplement. 15A[35] and 15C[35,36] was assumed to be covered in PPSV23; among children included in this analysis, 79% (27/34) of children were two years or older, and 26% (9/34) were on hydroxyurea. No significant effect of age, hydroxyurea and no significant interactions were noted in adjusted models. Models with children 0-9 years old were adjusted for age (0-2 vs. >two years) and hydroxyurea use (yes/no); those with children 2-9 years old adjusted for hydroxyurea use only. Three IPD with unknow PPSV23 vaccine history were excluded. Three Non-PCV13 IPD with unknow PPSV23 status were excluded.

Table 7: IPD incidence rates previously published among children with SCD

Study	Arm	Hb	Year	Age, years	(n/per-yrs.), n/1000 per-yrs
Miami[7]		SS	58-68	<2	(10/68.7), 145.6
		SS	58-68	2-3	(9/115.7), 77.8
		SS	58-68	4-9	(1/270.7), 3.7
		SS	58-68	10-19	(1/179.7), 5.6
		SS	58-68	20-29	(0/146.0), 0
		SS	58-68	30+	(0/83.1), 0
LAC-USC[4]		SS	<72	0-5	(29/634), 45.7
	IV abx	SS	>=72	0-5	(17/147), 115.6
CSSCD[79]		SS	79-85	<1	(12/188), 63.8
		SS	79-85	1	(17/268), 63.4
		SS	79-85	2	(17/296), 57.4
		SS	79-85	3	(3/334), 9.0
		SS	79-85	4	(5/346), 14.5
		SS	79-85	5	(4/345), 11.6
PROPS[5]	Placebo	SS	83-85	<1	(3/14.9), 201.3
		SS	83-85	1	(4/43.8), 91.3
		SS	83-85	2	(5/46.5), 107.5
		SS	83-85	3	(1/27.6), 36.2
		SS	83-85	0-3	(13/132.8), 97.9
	Penicillin	SS	83-85	<1	(0/12.2), 0
		SS	83-85	1	(1/45.9), 21.8
		SS	83-85	2	(0/48.2), 0
		SS	83-85	3	(1/29.8), 33.6
		SS	83-85	0-3	(2/136.1), 14.7
PROPS2[10]	Placebo	SS	88-93	4.7-8	(4/597), 6.7
	Penicillin	SS	88-93	4.7-8	(2/606), 3.3
PA/VA[49]		SS	92-98	<5	(30 /1232), 24.4
		SS	92-98	5–21	(10 /2876), 3.5
		SC	92-98	<5	(7 /533), 13.1
		SC	92-98	5–21	(0/1244), 0
8 centers[13]		SS	97-99	<1	(4/221), 18.1
		SS	97-99	1	(23/363), 63.4
		SS	97-99	2	(13/355), 36.6
		SS	97-99	3-4	(10/688), 14.5
		SS	97-99	0-4	(50/1627), 30.7
		SS	97-99	5-10	(18/1958), 9.2
		SS	97-99	0-10	(68/3585), 19.0
		SC	97-99	0-4	(6/445), 13.5
		SC	97-99	5-10	(0 /625), 0
TN/ABC[50]		SCD	95-99	<2	36.3
		SCD	95-99	<5	20.4
		SCD	95-99	>=5	1.6
		SCD	2000	<2	10.8
		SCD	2000	<5	30.1
		SCD	2000	>=5	1.7
		SCD	01-04	<2	3.4
		SCD	01-04	<5	1.3
		SCD	01-04	>=5	1
GA/ABC[17]		SS/SC	95-99	0-10	(44/2543), 17.3
		SS/SC	2000	0-10	(8/573), 14.0
		SS/SC	2001	0-10	(4/578), 6.9
		SS/SC	2002	0-10	(2/515), 3.9
USA/ABC[18]		SCD	98-99	0-4	22.7
		SCD	98-99	5-17	3.0
		SCD	00-04	0-4	5.9
		SCD	00-04	5-17	2.9
		SCD	05-09	0-4	5.4
		SCD	05-09	5-17	2.2

Hb: hemoglobin, yrs: years; per: person; abx: antibiotics

Table 8: Non-PCV13 IPD in children with SCD and IPD, serotype coverage by PPSV23, PCV15, PCV20 and PCV21/V116.

Clinical isolate data sources		PPSV23		PPSV23*		PCV15		PCV20		PCV21		Total	
		n	%	n	%	n	%	n	%	n	%	n	%
Ghana[41]	**Nasopharyngeal (NP)**	9	22%	14	34%	0	0%	11	27%	24	60%	40	100%
All isolates	**IPD**+NP**	27	22%	60	49%	8	7%	48	39%	95	77%	123	100%

Serotype 15C assumed covered in PCV20,[37] 6C and 15C in PCV21.[35]

*Vaccine related serotype 15A[35] and 15C[35,36] assumed to be covered in PPSV23.

**: IPD serotype data in children with SCD data from the present study and following references.[13,40,49,7150,72-78]