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Vaccine utilization and overwhelming post-splenectomy infection risk factors in two asplenia cohorts

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The spleen is a secondary lymphoid organ involved with immune surveillance of blood. Asplenia following splenectomy and functional asplenia due to Sickle Cell Disease (HbSS disease) are associated with invasive infections known as overwhelming post-splenectomy infections (OPSIs)[1,2]. OPSIs can be caused by several bacterial species including gram-positive *Streptococcus pneumoniae* as well as the gram-negative organisms *Neisseria meningitidis* and *Haemophilus influenzae* type B[2–4] for which the American College of Immunizations Practices (ACIP) recommends vaccination[5–7]. The rate of OPSIs in patients with asplenia in an Australian clinical registry was lower (1 OPSI every 2,778 patient years) than the rate of OPSIs prior to joining the registry (1 OPSI every 667 patient years) suggesting a benefit to immunization.[8,9] However, there are few other studies assessing which patients are most likely to develop OPSIs though risk factors may include failure to vaccinate, infection with *S. pneumoniae* nonvaccine serotypes, inadequate response to immunizations, and immunodeficiency.[8,10–12] We aimed to assess the rates of *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* OPSIs, overall time spent unvaccinated, and risk factors for individuals with OPSIs in two asplenia registries.

A retrospective analysis of two independent cohorts of Tricare beneficiaries with asplenia was performed. The first cohort was derived from the Department of Defense Joint Trauma Registry (DoDTR) of the Joint Trauma System (JTS)[13]. The JTS was developed to provide evidence-based improvement of combat casualty care, and the DoDTR facilitates analysis of combat casualties. The registry incorporates data from the point of injury forward in time or until the patient no longer has Tricare insurance. The DoDTR was queried on February 27, 2020 for service members who underwent splenectomy following combat trauma from January 1, 2000 to January 1, 2020 using ICD codes (see supplemental Table 1). Most individuals identified from the DoDTR were not active Tricare beneficiaries at the time of the query as only 44 out of 256 subjects from the DoDTR had a most recent encounter within 6 months of the query.

The second cohort was derived from a national capital region registry (NCRR) linked to the Military Health System (MHS) electronic medical record (EMR) and claims data accessed from the MHS population health portal. The NCRR includes military personnel, dependents, foreign nationals, and retirees who receive care in the national capital region. The NCRR was queried on April 30, 2021 for individuals with any form of asplenia including those with HbSS disease using ICD and CPT codes (see supplemental Table 1). All NCRR individuals at the time of the query were active Tricare beneficiaries.

Individuals in the DoDTR and NCRR were included if there was documentation of splenectomy or asplenia in a clinical encounter and the duration of follow up was greater than 30 days. Coded data were collected by review of subject charts. Data collected included demographics, microbiology reports, peripheral blood smear interpretations, immunology laboratory assessments, and vaccinations. OPSIs were defined by a *S. pneumoniae*, *N. meningitidis*, or *H. influenzae* positive cultures from immunologically protected sites such as blood and cerebral spinal fluid. Immunizations collected included pneumococcal polysaccharide (PPSV23), pneumococcal conjugate (PCV13), meningococcal conjugate (MCV4), meningococcal polysaccharide (MPSV4), meningococcal B (MenB), and *H. influenzae* type b (Hib).

In the DoDTR, 552 individuals were identified with splenic injury. Of the 552, 239 were excluded since no documentation of splenectomy was identified in their EMR, 9 of 552 were excluded due to partial splenectomy, 14 of 552 were excluded due to splenorrhaphy, and 34 of 552 were excluded due to lack of follow up beyond 30 days after splenectomy. Of the 552, 256 were confirmed to have asplenia with at least 30 days of follow up and were included in the analysis. In the NCRR, 338 individuals were identified with an asplenia ICD or CPT code. Of the 338, 167 were excluded since no documentation of asplenia was identified in the EMR. The remaining 171 of 338 were confirmed to have asplenia. All subjects had at least 30 days of follow up after splenectomy or 1 year of age if they had HbSS disease without splenectomy since nearly all patients with HbSS disease have splenic dysfunction by age 1[1].

Demographic data for both cohorts are shown in Table 1. 98% of subjects were men and 65% of subjects were women in the DoDTR and NCRR, respectively. Subjects in the DoDTR had a lower average age than subjects in the NCRR (25.17 versus 49.65-years old respectively). 100% of subjects in the DoDTR had asplenia from splenectomy following trauma compared to only 10.5% in the NCRR. 23.4% of subjects in the NCRR had asplenia related to HbSS disease. The average duration of clinical follow up after development of asplenia was nearly three times lower in the DoDTR compared to the NCRR cohort (5.37 versus 19.45 years, respectively). There were five OPSI events in the NCRR cohort corresponding to a prevalence of 1 OPSI per 669 patient years. There were no OPSI events in the DoDTR cohort in 1375 patient years. The rate of immunization was higher in the NCRR compared to DoDTR for PCV13 (84% vs 15%), PPSV23 (71% vs 69%), HiB (68% vs 65%), and MenB (38% vs 5%). More subjects in the DoDTR compared to NCRR were immunized for MCV4/MPS4 (91% vs 83%).

The total time spent unvaccinated was higher in the NCRR cohort as compared to the DoDTR for all vaccines assessed (Figure 1). In the NCRR cohort, 4 subjects had an invasive pneumococcal and 1 subject had invasive *H. influenzae* infection (Table 2). For the pneumococcal OPSIs, there was a prevalence of 1 OPSI per 695 PCV13-unvaccinated patient years and per 526 PPSV23-unvaccinated patient years. One of the 4 subjects with an invasive pneumococcal infection was immunized with PCV13 and 4 of 4 were immunized with PPSV23 prior to developing the OPSI. Three of the 4 vaccinated with PPSV23 were immunized within 5 years of developing their OPSI. For *H. influenzae* OPSIs, there was a prevalence of 1 OPSI per 434 Hib-unvaccinated patient years. The subject with *H. influenzae* OPSI was immunized with HiB prior to the OPSI and demonstrated *H. influenzae* B antibody IgG titer of 5.8 mcg/mL several years later (protective titer > 0.15 mcg/mL). Two of the 4 subjects with an invasive pneumococcal OPSI had evidence of selective IgM deficiency (SIGMD). SIGMD was associated with reduced responses to polysaccharide PPSV23 antigens in both subjects and low isohemagglutinin titers in 1 subject (see supplemental Table 2). There was no documentation in the EMR that the *S. pneumoniae* isolates had been serotyped.

Limitations of this study included the retrospective design and lack of pneumococcal serotyping data. In addition, the small number of OPSI events make it difficult to draw firm conclusions on OPSI risk factors in patients undergoing splenectomy or HbSS disease. Nonetheless, there are several interesting findings. First, OPSIs in patients with asplenia are rare, consistent with prior

reports[8,9], with 1 OPSI per 669 patient years in the NCRR cohort and 0 OPSI per 1375 patient years in the DoDTR cohort. The lower rate of OPSI in the DoDTR compared to the NCRR may reflect the relative health of the active-duty military population as well as the fewer total days spent unimmunized. The low OPSI rate in both cohorts is notable especially when considering the total number of days spent unvaccinated for each vaccine. Second, the data we present suggests a possible benefit to PCV13 immunization. For instance, the cumulative time spent unvaccinated was 2.5 times longer for PCV13 in the NCRR cohort (1,190,862 days) compared to the DoDTR cohort (482,511 days), and 3 of the 4 subjects with invasive pneumococcal infection had not been immunized with PCV13 prior to the OPSI. Third, most patients with an *S. pneumoniae* OPSI are not eligible under CDC and state rules for pneumococcal serotyping. Therefore, there is a need to develop a national resource for pneumococcal serotyping for patients with OPSI to differentiate between vaccine nonresponse and emergence of pneumococcal nonvaccine serotype infection. Finally, 2 of the 5 patients with OPSI in the NCRR cohort demonstrated SIGMD suggesting a possible link between SIGMD and OPSI. Prior reports have shown a high rate of poor response to pneumococcal polysaccharide antigens in patients with SIGMD compared to the rates of poor response in the general population[14,15]. Also, a link between OPSI and problems in humoral immunity has been suggested for Autoimmune Lymphoproliferative Syndrome[10] as well as in two patients with lack of response to pneumococcal polysaccharide antigens[11]. In summary, OPSIs are rare in patients with asplenia, even in those who are unvaccinated suggesting the number needed to immunize is high to prevent one OPSI infection, pneumococcal isolate serotyping would benefit patients with OPSI, and the rare patients with OPSIs should be evaluated for occult humoral immunodeficiency.

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Characteristic	NCRR	DoDTR
Subjects	171	256
Average age in years (range)	49.65	25.17
Male	60 (35%)	251 (98.0%)
HJ bodies	45 (26.3%)	92 (35.9%)
Etiology of asplenia		
HbSS disease	40 (23.4%)	0
Splenectomy	131 (76.6%)	256 (100%)
Other neoplasms	29 (17%)	0
Pancreatic neoplasms	26 (15.2%)	0
Trauma	18 (10.5%)	256 (100%)
Immune thrombocytopenia	18 (10.5%)	0
Other	40 (23.3%)	0
Total patient years with asplenia	3344.66	1374.56
Average patient years with asplenia (range)	19.45 (0.58-64.42)	5.37 (0.5-16)
OPSI events	5	0
Immunizations		
PCV13 immunized	145/171 (84%)	17/256 (15%)
PPSV23 immunized	121/171 (71%)	117/256 (69%)
HiB immunized	116/171 (68%)	168/256 (65%)
MCV4/MPS4 immunized	142/171 (83%)	234/256 (91%)
MenB immunized	65/171 (38%)	4/256 (5%)

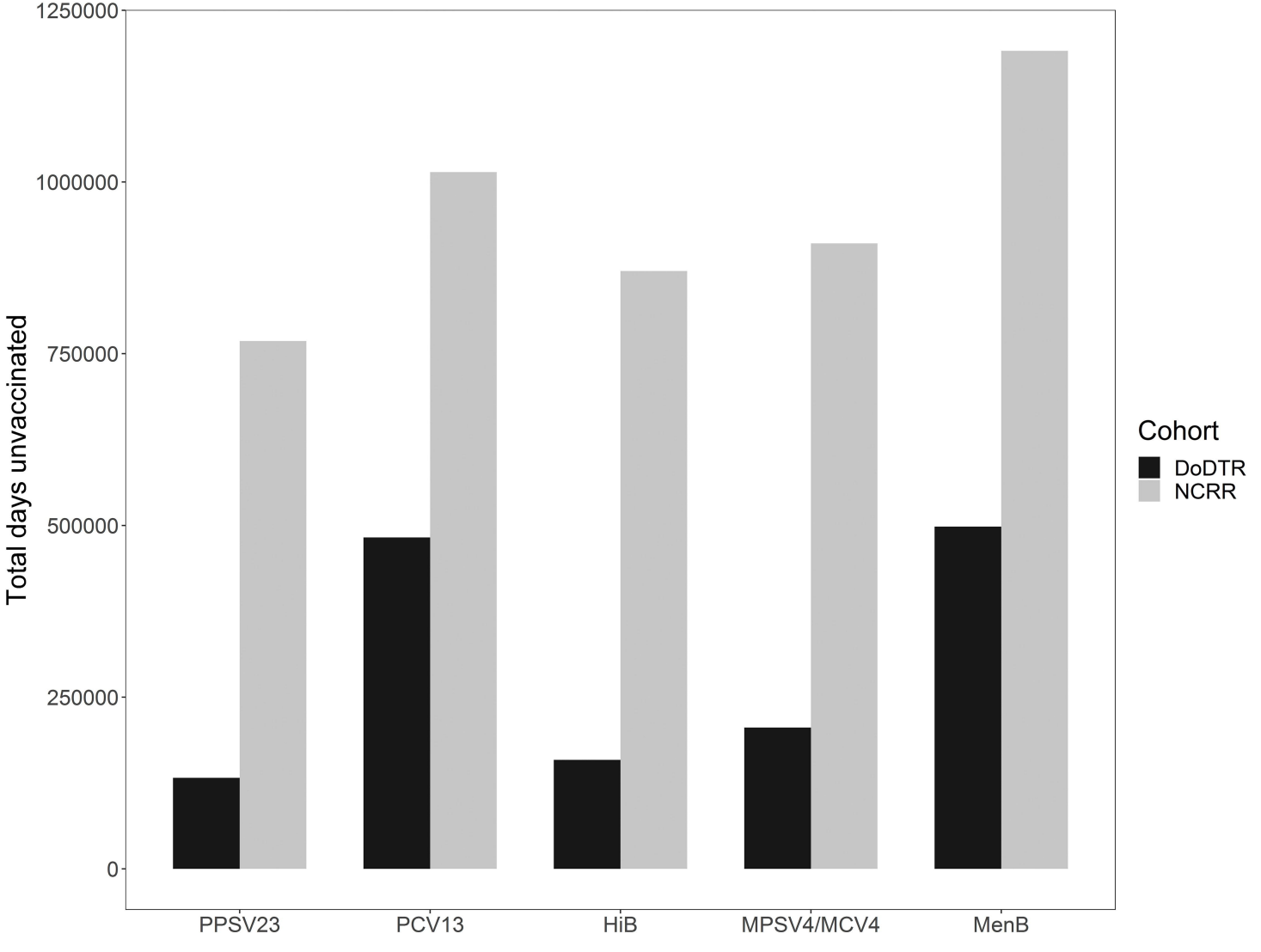
Table 1. Demographics of NCRR and DoDTR Cohorts

				Immunizations prior to OPSI*			
Age^/Sex	**Asplenia Etiology**	**Years to OPSI**	**Infection**	**PCV13**	**PPSV23**	**Hib**	**Immunodeficiency Diagnoses**
58/M	Splenectomy Pancreatic Neoplasm	4.6	*H. influenzae* bacteremia	n/a	n/a	Yes	n/a
53/F	Splenectomy Pancreatic Neoplasm	6	*S. pneumoniae* meningitis	No	Yes	n/a	Selective IgM deficiency
13/F	Splenectomy Hematologic Malignancy	32	*S. pneumoniae* bacteremia	No	Yes**	n/a	Selective IgM deficiency
1/M	HbSS	28.4	*S. pneumoniae* bacteremia and olecranon bursitis	No	Yes**	n/a	n/a
1/F	HbSS	4.9	*S. pneumoniae* bacteremia	Yes	Yes**	n/a	n/a

Table 2. Description of Subjects with OPSIs.
^ Age corresponds to age at splenectomy or age 1 where asplenia is present in HbSS disease
* Prior immunizations are listed for the organism underlying the OPSI
** PPSV23 was administered within 5 years of the OPSI

FIGURE LEGEND

Figure 1: Cumulative days spent unvaccinated for each vaccine in each cohort. The sum of the days spent unvaccinated following development of asplenia for all subjects in each cohort for each vaccine was determined. The Y-axis corresponds to the total days spent unvaccinated and the X-axis corresponds to each vaccine. The bars corresponding to the DoDTR cohort are in dark gray and the bars corresponding to the NCRR cohort are in light gray. Conjugate and polysaccharide meningococcal vaccines rates were combined since the ACIP has not recommended one over another. Time spent unvaccinated for each vaccine or vaccine series was defined by the difference in days between splenectomy and either a) the date of first immunization (PCV13, PPSV23, Hib), last immunization in series (MCV4/MPSV4, MenB), or last encounter date in the EMR if no vaccine was administered. In patients with HbSS disease, the date of the subject's first birthday was used in place of the date of splenectomy.


1250000
1000000
750000
500000
250000
0
Total days unvaccinated
PPSV23
PCV13
HiB
MPSV4/MCV4
MenB
Cohort
DoDTR
NCRR

Code	Description	National Capital Region Registry	DoD Trauma Registry
ICD9 41.5	Total splenectomy	Y	Y
ICD9 41.42	Excision of lesion or tissue of spleen	Y	
ICD9 41.43	Partial splenectomy		Y
ICD9 865	Spleen injury NFS closed		Y
ICD9 865.01	Spleen hematoma without rupture of capsule closed		Y
ICD9 865.02	Spleen injury with rupture of capsule closed		Y
ICD9 865.03	Spleen laceration extending into parenchyma closed		Y
ICD9 865.04	Spleen laceration with massive parenchymal disruption closed		Y
ICD9 865.09	Spleen injury other closed		Y
ICD9 865.11	Spleen hematoma without rupture of capsule open		Y
ICD9 865.12	Spleen injury with rupture of capsule open		Y
ICD9 865.13	Spleen laceration extending into parenchyma open		Y
ICD9 865.14	Spleen laceration with massive parenchymal disruption open		Y
ICD9 865.19	Spleen injury other open		Y
ICD9 282.41	Sickle-cell thalassemia without crisis	Y	
ICD9 282.42	Sickle-cell thalassemia with crisis	Y	
ICD9 282.5	Sickle-cell trait	Y	

ICD9 282.60	Sickle-cell disease, unspecified	Y	
ICD9 282.61	Hb-SS disease without crisis	Y	
ICD9 282.62	Hb-SS disease with crisis	Y	
ICD9 282.63	Sickle-cell/Hb-C disease without crisis	Y	
ICD9 282.68	Other sickle-cell disease without crisis	Y	
ICD9 759.0	Anomalies of spleen	Y	
ICD10 07BP0ZX	Excision of spleen, open approach, diagnostic		Y
ICD10 07BP0ZZ	Excision of spleen, open approach	Y	Y
ICD10 07BP4ZZ	Excision of spleen, percutaneous endoscopic approach	Y	Y
ICD10 07TP0ZZ	Resection of spleen, open approach	Y	
ICD10 07TP4ZZ	Resection of Spleen, Percutaneous Endoscopic Approach	Y	
ICD10 S36.00XA	Unspecified injury of spleen, initial encounter		Y
ICD10 S36.020A	Minor contusion of spleen, initial encounter		Y
ICD10 S36.021A	Major contusion of spleen, initial encounter		Y
ICD10 S36.029A	Unspecified contusion of spleen, initial encounter		Y
ICD10 S36.030A	Superficial (capsular) laceration of spleen, initial encounter		Y
ICD10 S36.031A	Moderate laceration of spleen, initial encounter		Y
ICD10 S36.032A	Major laceration of spleen, initial encounter		Y
ICD10 S36.039A	Unspecified laceration of spleen, initial encounter		Y

ICD10 S36.09XA	Other injury of spleen, initial encounter		Y
ICD10 D57.00	Hb-SS disease with crisis, unspecified	Y	
ICD10 D57.01	Hb-SS disease with acute chest syndrome	Y	
ICD10 D57.1	Sickle-cell disease without crisis	Y	
ICD10 D57.219	Sickle-cell/Hb-C disease with crisis, unspecified	Y	
ICD10 D57.3	Sickle-cell trait	Y	
ICD10 D57.419	Sickle-cell thalassemia, unspecified, with crisis	Y	
ICD10 D57.80	Other sickle-cell disorders without crisis	Y	
ICD10 D57.819	Other sickle-cell disorders with crisis, unspecified	Y	
ICD10 D73.0	Hyposplenism	Y	
ICD10 D73.5	Infarction of spleen	Y	
ICD10 Q89.01	Asplenia (congenital)	Y	
ICD10 Q89.09	Congenital malformations of spleen	Y	
ICD10 Z90.81	Acquired absence of spleen	Y	
CPT 38100	Excision Procedures on the Spleen	Y	
CPT 38120	Laparoscopic Procedures on the Spleen	Y	

Table S1. ICD10 and ICD9 Diagnosis and Procedure Codes to Identify Asplenia in the National Capital Region Registry (NCRR) and DoD Trauma Registry (DoDTR)

Age^/Sex	IgM (70-400 mg/dL)	Pre-PPSV23 pneumococcal serology titers >1.3 mg/mL; >0.35 mg/mL	Post-PPSV23 (4-6 weeks) pneumococcal serology titers >1.3 mg/mL; >0.35 mg/mL
58/M	129; 135	23/23; 23/23	Not performed
53/F*	<25; <25	0/23; 5/23	2/23; 9/23
		0/11 (0%) PPSV23 serotypes > 1.3 mg/mL	0/11 (0%) PPSV23 serotypes > 1.3 mg/mL
		0/11 (9%) PPSV23 serotypes > 0.35 mg/mL	1/11 (9%) PPSV23 serotypes > 0.35 mg/mL
13/F*	28; 29	10/23; 18/23	12/23; 18/23
		2/11 (18%) PPSV23 serotypes > 1.3 mg/mL	2/11 (18%) PPSV23 serotypes > 1.3 mg/mL
		6/11 (54%) PPSV23 serotypes > 0.35 mg/mL	6/11 (54%) PPSV23 serotypes > 0.35 mg/mL
1/M	121; 66	17/23; 22/23	Not performed
1/F	75; 73	12/23; 22/23	Not performed

Table S2. Immunologic data of subjects with OPSI.

^ Age corresponds to age at splenectomy or age 1 where asplenia is present in HbSS disease

* These two subjects had post-PPSV23 immunization titers drawn due to low pre-PPSV23 titers.

Note: All subjects had normal levels of immunoglobulin G and A (not shown). All subjects had been immunized with PCV13 prior to PPSV23 vaccine titer assessments and PPSV23 has 11 serotypes that are not found in PCV13. A cutoff of 1.3 mcg/mL for each pneumococcal serotype is the current Practice Parameter recommendation for immunity[1] while a cutoff of 0.35 mcg/mL may be more specific for invasive disease[2].

Note: The subject age 53 at splenectomy was blood type B+ and had very low isohemagglutinin titers (IgG anti-A titer 1:2 and IgM anti-A 1:4). All other subjects had isohemagglutinin titers within reference ranges.

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