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

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 (OPSI).[1,2] OPSI 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 OPSI in patients with asplenia in an Australian clinical registry was lower (1 OPSI every 2,778 patient years) than the rate of OPSI 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 OPSI though risk factors may include failure to vaccinate, infection with *S. pneumoniae* non-vaccine serotypes, inadequate response to immunizations, and immunodeficiency.[8,10–12] We aimed to assess the rates of *S. pneumoniae, N. meningitidis,* and *H. influenzae* OPSI, the overall time spent unvaccinated, and risk factors for individuals with OPSI 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 *Online Supplementary Table S1*). Most individuals identified from the DoDTR were not active Tricare beneficiaries at the time of the query as only 44 of 256 subjects from the DoDTR had a most recent encounter within 6 months of the query.

Table 1. Demographics of National Capital Region Registry (NCRR) and Department of Defense Joint Trauma Registry (DoDTR) Cohorts.

Characteristic	NCRR	DoDTR
Subjects, N	171	256
Average age in years	49.65	25.17
Male, N (%)	60 (35)	251 (98.0)
HJ bodies, N (%)	45 (26.3)	92 (35.9)
Etiology of asplenia, N (%)		
HbSS disease	40 (23.4)	0
Splenectomy, N (%)	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	3,344.66	1,374.56
Average patient years with asplenia (range)	19.45 (0.58-64.42)	5.37 (0.5-16)
OPSI events, N	5	0
Immunizations, N/N (%)		
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)

HJ bodies: Howell–Jolly bodies; HbSS: sickle cell disease; OPSI: overwhelming post-splenectomy infections; PCV13: pneumococcal conjugate vaccine 13; PPSV23: pneumococcal polysaccharide vaccine 23; HiB: *Haemophilus influenzae* type B vaccine; MCV4/MPS4: meningococcal vaccines; MenB: meningococcal B vaccine.

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 *Online Supplementary Table S1*). 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. OPSI 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, nine 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. Ninety-eight percent 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 *vs*. 49.65 years old respectively). One hundred percent 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 *vs*. 19.45 years, respectively). There were five OPSI events in the NCRR cohort corresponding to a prevalence of one OPSI per 669 patient years. There were no OPSI events in the DoDTR cohort in 1,375 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

Table 2. Description of subjects with overwhelming post-splenectomy infections.

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

^Age corresponds to age at splenectomy or age 1 year old where asplenia is present in sickle cell disease (HbSS). *Prior immunizations are listed for the organism underlying the overwhelming post-splenectomy infections (OPSI). **PPSV23 was administered within 5 years of the OPSI. PCV13: pneumococcal conjugate vaccine 13; PPSV23: pneumococcal polysaccharide vaccine 23; HiB: *Haemophilus influenzae* type B vaccine; F: female; M: male; IgM: immunoglobulin M; NA: not applicable.

cohort as compared to the DoDTR for all vaccines assessed (Figure 1). In the NCRR cohort, four subjects had an invasive pneumococcal and one subject had invasive *H. influenzae* infection (Table 2). For the pneumococcal OPSI, there was a prevalence of one OPSI per 695 PCV13-unvaccinated patient years and per 526 PPSV23-unvaccinated patient years. One of the four subjects with an invasive pneumococcal infection was immunized with PCV13 and four of four were immunized with PPSV23 prior to developing the OPSI. Three of the four vaccinated with PPSV23 were immunized within 5 years of developing their OPSI. For *H. influenzae* OPSI, there was a prevalence of one 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 four 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 one subject (see *Online Supplementary Table S2*). 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, OPSI in patients with asplenia are rare, consistent with prior reports,[8,9] with one OPSI per 669 patient years in the NCRR cohort and zero OPSI per 1,375 patient years in the DoDTR cohort. The lower rate

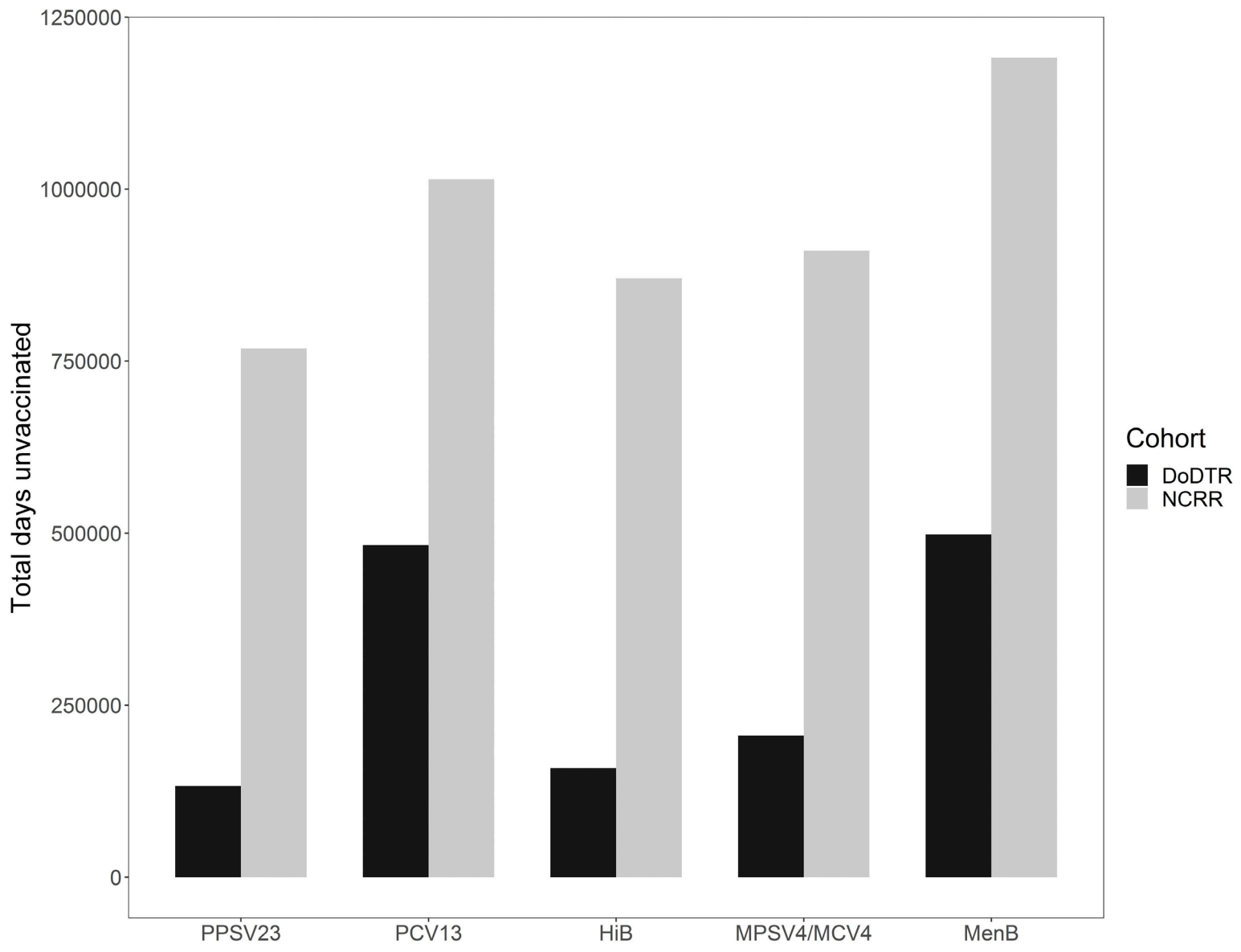

Figure 1. Cumulative days spent unvaccinated for each vaccine in each cohort. The sum of the days spent unvaccinated following development of asplenia for all subjects in each cohort for each vaccine was determined. The Y-axis corresponds to the total days spent unvaccinated and the X-axis corresponds to each vaccine. The bars corresponding to the Department of Defense Joint Trauma Registry (DoDTR) cohort are in dark gray and the bars corresponding to the National Capital Region Registry (NCRR) cohort are in light gray. Conjugate and polysaccharide meningococcal vaccines rates were combined since the American College of Immunizations Practices 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 the date of first immunization (PCV13, PPSV23, Hib), last immunization in series (MCV4/MPSV4, MenB), or last encounter date in the electronic medical record if no vaccine was administered. In patients with sickle cell (HbSS) disease, the date of the subject's first birthday was used in place of the date of splenectomy. PCV13: pneumococcal conjugate vaccine 13; PPSV23: pneumococcal polysaccharide vaccine 23; HiB: *Haemophilus influenzae* type B vaccine; MCV4/MPS4: meningococcal vaccines; MenB: meningococcal B vaccine.

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 (482,511days), and three of the four 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 non-response and emergence of pneumococcal non-vaccine serotype infection. Finally, two of the five 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, OPSI 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 OPSI should be evaluated for occult humoral immunodeficiency.

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Contributions

NB, MS, VKR, MB and RC designed the study. MS, MM, QW, WH, and NB collected the data. MS, MM, QW, NW and NB analyzed the data. MS and NB wrote the manuscript with input from all co-authors. The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of Uniformed Services University, National Institutes of Health or the Department of Health and Human Services, Walter Reed National Military Medical Center, Brooke Army Medical Center, the US Army Medical Department, the US Army Office of the Surgeon General, the Defense Health Agency, the Departments of the Air Force, Navy, Army, or the Department of Defense, or the US Government.

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Data-sharing statement

The data that support the findings of this study are available upon reasonable request to the corresponding author.

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