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MAJOR ARTICLE

A Single-Center Prospective Cohort Study on Postsplenectomy Sepsis and its Prevention

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Background. This study evaluated the impact of a dedicated outpatient service on vaccination uptake after splenectomy and on the incidence of postsplenectomy sepsis.

Methods. From 2009 to 2016 at the University Hospital Freiburg (Germany), asplenic patients were referred to a dedicated outpatient service, provided with comprehensive preventive care including vaccinations, and enrolled in a prospective cohort study. The impact of the service on vaccination uptake and the occurrence of severe sepsis/septic shock was compared between patients who had splenectomy (or were asplenic) within 3 months of study entry ("early study entry") and those who had splenectomy (or were asplenic) >3 months before study entry ("delayed study entry").

Results. A total of 459 asplenic patients were enrolled, and 426 patients were followed prospectively over a median period of 2.9 years. Pneumococcal vaccine uptake within 3 months of splenectomy or first diagnosis of asplenia was 27% vs 71% among delayed study entry and early study entry patients, respectively ($P < .001$). Forty-four episodes of severe sepsis or septic shock occurred in study patients: 22 after study entry and 22 before study entry. *Streptococcus pneumoniae* was more frequent among sepsis episodes that occurred before study entry (8/22) than after study entry (1/22 episodes). For episodes occurring after study entry, only a higher Charlson comorbidity index score was significantly associated with severe sepsis/septic shock postsplenectomy.

Conclusions. With dedicated outpatient care, high uptake of pneumococcal vaccination postsplenectomy was achieved. Sepsis episodes were largely of nonpneumococcal etiology in patients who had received dedicated postsplenectomy care.

Keywords. asplenia; postsplenectomy sepsis; vaccination.

Asplenia and splenic dysfunction are associated with an immunodeficiency that predisposes patients to a life-threating sepsis syndrome called either postsplenectomy sepsis or overwhelming postsplenectomy infection (OPSI) [1]. In Germany, ~8000 splenectomies are performed annually [2]. In the United Kingdom, prevalence of asplenia in the adult population has been documented at 0.4%–0.6% [3]. Earlier systematic reviews have reported >50% of OPSI cases to be caused by *Streptococcus pneumoniae* [4]. However, most of these studies predate the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13), which in most countries, including Germany, is now recommend for this risk group, in conjunction with the 23-valent pneumococcal polysaccharide vaccine (PPV-23) [5]. Recent data on the epidemiology of infections in patients with functional and anatomic asplenia are rare. The data that do exist largely come from retrospective cohort studies [6, 7] that have relied on hospital discharge codes—an approach that may cause bias due to variability in coding quality [8]. To our knowledge, no study performed to date prospectively has analyzed the epidemiology of severe infection and sepsis after splenectomy while also engaging in active, patient-level follow-up.

Despite guidelines recommending vaccination against *S. pneumoniae, N. meningitidis,* and *Haemophilus influenzae* B for patients with anatomic or functional asplenia, vaccination rates for these infections remain unsatisfactory [9–11]. To improve the quality of preventive care for splenectomized patients, in 2009 the University Medical Center Freiburg established a dedicated outpatient service. All patients diagnosed with splenectomy/asplenia were referred to an outpatient clinic that focused on providing counseling both to prevent postsplenectomy infection and to recommend and deliver preventive measures.

The goals of the present study were to assess the impact of a dedicated care program on the uptake of vaccinations

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recommended for splenectomized patients and the impact of this intervention on the incidence, as well as clinical and microbiological features, of severe infections and sepsis postsplenectomy.

METHODS

Study Design, Setting, and Participants

This monocentric, prospective cohort study was conducted at the University Medical Center Freiburg, a tertiary care institution with 1600 hospital beds that serves the southwest region of the German state of Baden-Württemberg.

Between January 2009 and December 2016, all surgical intensive care units at the University Medical Center Freiburg kept screening logs of patients who had undergone abdominal surgery for splenectomy and provided study staff with the screening logs on a biweekly basis. All eligible patients received a written invitation to an outpatient service dedicated to delivering comprehensive infection prevention postsplenectomy. These patients were considered "early study entry." Also eligible for the study were patients referred to the outpatient clinic between 2009 and 2016 for splenectomies that had been performed >3 months before referral either in the study center or in surrounding regional hospitals. These patients were designated "delayed study entry." Patients with an underlying disease considered to be rapidly fatal (ie, a life expectancy <3 months) were deemed ineligible for the study. During their outpatient clinic visits, patients received counseling from a physician and supporting nurse regarding the risk of infection after splenectomy, and they were given alert cards, along with an educational kit describing available preventive measures. Standby antibiotics routinely were prescribed to splenectomized or asplenic patients with the following exceptions: (1) patients with immunocompromising conditions other than asplenia and (2) patients with a previous postsplenectomy sepsis. These 2 patient groups received permanent antibiotic prophylaxis, as recommended by German guidelines [12]. During the baseline visit, missing vaccine doses were delivered according to national recommendations [5, 12]. If study patients were still hospitalized 14 days postsplenectomy, then a visit to the outpatient service was scheduled before hospital discharge.

During the study period, the vaccination guidelines of the German Standing Committee for Vaccination Recommendations (STIKO) regarding pneumococcal and meningococcal vaccinations in asplenic patients changed substantially. The changes included a switch to sequential pneumococcal vaccination with the 13-valent pneumococcal conjugate vaccine, followed by the 23-valent pneumococcal polysaccharide vaccine; a switch to the tetravalent meningococcal conjugate vaccine; and the inclusion of meningococcus type B vaccination. In its most recent guidelines update, STIKO recommended that pneumococcal vaccine–naïve adults receive a single dose of the 13-valent pneumococcal conjugate vaccine (PCV13), followed by a dose of the 23-valent pneumococcal polysaccharide vaccine (PPV23) 6–12 months later. Revaccination with PPV23 was recommended every 6 years. In addition, 2 doses of a 4-valent meningococcal conjugate vaccine given 2 months apart were recommended. The 4-component MenB vaccine (4CMenB, Bexsero) was recommended as a single dose, depending on the physician's choice. A single *Haemophilus influenzae* type B vaccination for vaccine-naïve individuals was also recommended [5, 12]. In patients receiving immunosuppressive medication or chemotherapy, vaccination was given in accordance with physican judgment and current guidelines [12]. Follow-up visits were either scheduled in the outpatient clinic or at the primary care provider, depending upon the patient's preference. Further follow-up was done by phone interview at 3 months, 12 months, and then again at the end of the study. If a patient could not be contacted directly, then we contacted the patient's legal representative or primary care physician to obtain information for the follow-up visit.

The study was approved by the ethics committee of the University Medical Center Freiburg and is registered in the German Clinical Trials Register (identifier DRKS00004332). Informed written consent was obtained from all participants before study entry.

Variables Collected

During the baseline study visit, demographic variables, comorbid illness, and Charlson comorbidity index [13] were documented. In addition, vaccination status for pneumococcal vaccines, meningococcal vaccines, and the *H. influenzae* B conjugate vaccine was assessed by reviewing written vaccination records. Postsplenectomy infections leading to hospital admission were assessed retrospectively via structured patient interviews, as well as via review of medical records (University Medical Center Freiburg) and discharge records (other hospitals). To confirm asplenia, blood films were obtained from all patients and examined by microscopy for the presence of Howell-Jolly inclusion bodies.

During the follow-up patient interviews, information concerning the type, severity, and timing of infections, immunosuppressive medication or chemotherapy, and vaccination status was obtained. All reported hospitalizations relating to infection were validated using medical discharge records and were reviewed for plausibility by 2 experienced infectious diseases specialists (S.R. and C.T.).

Definitions

Early study entry was defined as study inclusion and receipt of dedicated postsplenectomy care within 3 months after splenectomy or incident diagnosis of asplenia. Delayed study entry, on the other hand, was defined as study inclusion later than 3 months after splenectomy. Severe infections in asplenic patients were defined as ones that required hospitalization for more than 48 hours. Severe sepsis and septic shock were defined by the

criteria published by Levy et al. [14]. Splenectomy was defined as the surgical removal of the spleen. Functional hyposplenia and asplenia were defined as loss of splenic function due to underlying comorbidity, radiation therapy, or splenic embolization leading to the presence of erythrocyte Howell-Jolly inclusions bodies [1]. For patients with functional hyposplenia or asplenia, we considered the date of splenectomy to be the date of first documentation of the hyposplenia diagnosis; for congenital asplenia, we used the date of birth. Therapeutic splenectomies, splenectomies for malignant disease, splenomegaly, and benign procedures were considered elective, whereas splenectomies for splenic trauma, infection, pancreatitis, and accidental splenic laceration during abdominal surgery were considered nonelective. Unless specifically mentioned in the text, the term "splenectomy" also included functional asplenia/hyposplenia. Ongoing or recent chemotherapy was defined as antineoplastic chemotherapy within the last 3 months before the baseline study visit.

Because of the multiple changes in vaccine recommendations during the study period, vaccine exposure for pneumococcal vaccines was defined as the receipt of at least 1 dose of the 23-valent pneumococcal polysaccharide vaccine (PPV23) or the 13-valent pneumococcal conjugate vaccine (PCV13). For meningococcal vaccines, we defined vaccine exposure as the receipt of at least 1 dose of the quadrivalent meningococcal polysaccharide vaccine (MPSV4), a monovalent or quadrivalent meningococcal conjugate vaccine (MenC or MenACWY), or a meningococcal serogroup B vaccine (MenB).

Statistical Analysis

We calculated the proportion of patients vaccinated against pneumococci, meningococci, and *H. influenzae* by using a denominator of all patients with a baseline study visit. For the calculation of vaccination uptake during follow-up, the denominator was all patients with follow-up visits available. We described crude incidence rates of infections leading to hospitalization and severe sepsis/septic shock during prospective follow-up per 1000 patient-years of observation (PYO) with 95% confidence intervals.

A Cox regression model was used to assess the influence of demographic variables, comorbidity, and pneumococcal vaccination on the time before the first sepsis episode following study entry. We adjusted the model for age, gender, time after splenectomy (at study entry), splenectomy indication, receipt of immunosuppression/chemotherapy, and pneumococcal vaccination exposure. As a sensitivity analysis, a Cox regression model was performed for the combined outcomes of severe sepsis/septic shock due to *S. pneumoniae* and severe sepsis/septic shock of unknown microbial etiology. Time of follow-up since splenectomy was left-censored for patients who entered the cohort postsplenectomy. Statistical analyses were performed using the SAS software package (SAS Institute, Cary, NC, USA). All tests were 2-sided, and P values <.05 were considered statistically significant.

RESULTS

Study Population and Baseline Characteristics

Between January 2009 and August 2016, a total of 459 patients were enrolled in the study (Figure 1). Of these, 268 were enrolled in the study within 3 months after splenectomy ("early study entry"). In 191 patients, the interval between splenectomy and study enrollment was longer ("delayed study entry"). The baseline characteristics of the study population are shown in Table 1. The most frequent indications for splenectomy were solid or hematological malignancies (39% of the cases), followed by splenic trauma, therapeutic splenectomy, and benign abdominal tumors (Table 1). Two percent of patients were included in the cohort for functional hyposplenia or asplenia.

The most common comorbid conditions were diabetes mellitus, coronary artery disease, and chronic renal disease. Fifty-four percent of patients had a Charlson Comorbidity Index of 2 or higher, and 97 (21%) received therapeutic immunosuppression or antineoplastic chemotherapy during the baseline visit. In addition to asplenia, 12% of patients had chronic medical conditions predisposing them to pneumococcal disease, as defined by Germany's Standing Committee for Vaccination (STIKO), and 46% had immunocompromising conditions considered by the STIKO to be high risk for pneumococcal infection (Table 1).

Patients with delayed entry to the study cohort differed from patients with early entry with respect to their underlying risk status, median time since splenectomy, Charlson comorbidity index score, and indication for splenectomy (Table 1).

Vaccination Status for Vaccines Indicated for Asplenic Patients

Vaccination status was assessed at baseline and during follow-up (Table 2). Among the 268 patients with early study entry, 71% received at least 1 single dose of a pneumococcal vaccine, 52% received a meningococcal vaccine, and 69% received a vaccine against *H. influenzae* type B within 3 months after splenectomy (Table 2).

By contrast, patients with delayed study entry—ones who therefore did not receive dedicated preventive care directly following splenectomy—had significantly lower early coverage for pneumococcal vaccination (27%), meningococcal vaccination (17%), and HiB vaccination (18%) (Table 2, Figure 2).

A total of 298 (64%) splenectomies were considered elective. Of those patients, 52 (17%) were vaccinated at least 14 days before surgery. Among the patients who entered in the study early after splenectomy, 39 patients (15%) received antineoplastic chemotherapy within 3 months before the study baseline visit and therefore had a relative contraindication to vaccination. During the follow-up period, vaccination uptake increased, reaching a cumulative pneumococcal vaccine uptake of 90% (Figure 2).

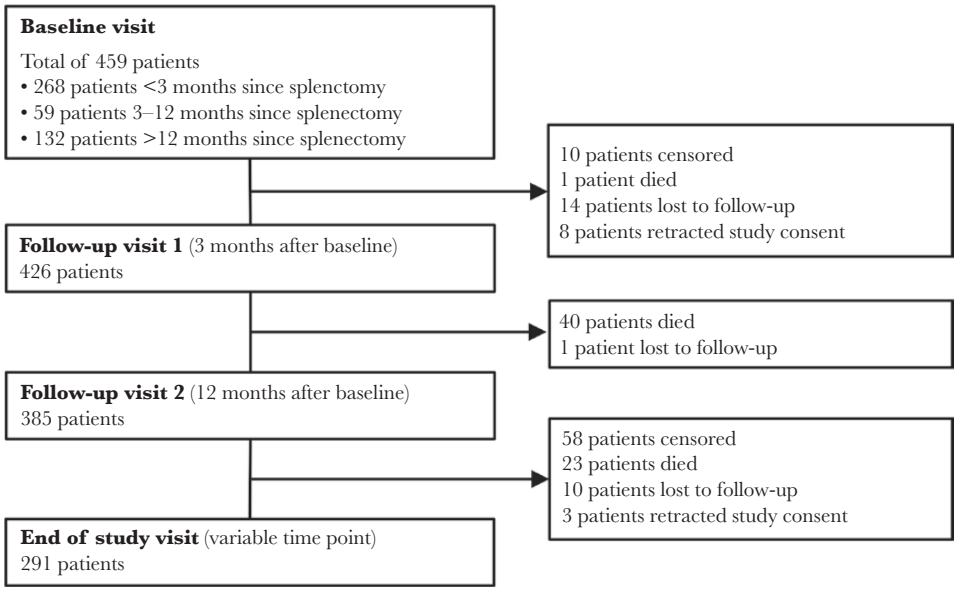

Figure 1. Overview of the study flow. Data on the number of patients who were eligible for the study but declined to participate were not collected.

Incidence of Severe Infections and Sepsis

Among the 426 patients with a minimum prospective follow-up time of 3 months, the median duration of follow-up (interquartile range [IQR]) was 2.9 (1.3–4.7) years (range, 3 months to 7.7 years). Of these 426 patients, 100 developed 164 infections leading to hospitalization over a follow-up of 1445 PYO. This resulted in an incidence rate of 113 infection-related admissions per 1000 PYO. Of the infections leading to hospital admission, 142 infections in 81 patients did not meet the criteria for severe sepsis/septic shock, whereas 19 patients developed 22 episodes of severe sepsis/septic shock (incidence rate, 13/1000 PYO; 95% confidence interval, 8–20).

The median time from splenectomy to first episode of severe sepsis (IQR) was 3.1 1.1–4.6) years (range, 0.2 to 17.0 years). Of the 19 first episodes of severe sepsis/septic shock, 2 occurred during the 3 months after the operation. In the 191 patients with delayed study entry, 22 episodes of severe sepsis or septic shock occurred before study inclusion. Information on these sepsis episodes was collected retrospectively. For these sepsis episodes, the median time from splenectomy to infection (IQR) was 4.0 (1–13) years (range, 0.8 to 29 years). As the degree of underascertainment for the retrospectively documented sepsis episodes was unknown, we did not calculate incidence rates.

Clinical and Microbiological Features of Infections After Splenectomy

During prospective follow-up, the most frequent foci of severe sepsis/septic shock were the lower respiratory tract and urinary tract (Table 3). By contrast, primary bacteremia accounted for 32% of episodes of severe sepsis in patients before study entry (Table 3).

In 43% of patients with severe sepsis/septic shock during prospective follow-up, a causative pathogen was reported. The most common pathogens were *Escherichia coli* and *Klebsiella* spp. *S. pneumoniae* accounted for just 1 sepsis episode (Table 3). The patient with this case of pneumococcal sepsis had been vaccinated with PPV23 14 months earlier. In episodes of severe sepsis or septic shock occurring before study entry, *S. pneumoniae* accounted for 8 (36%) episodes. Of the 8 patients with pneumococcal sepsis, 1 had received PPV23 before sepsis, whereas the remaining 7 patients were unvaccinated.

Risk Factors for Severe Sepsis/Septic Shock After Splenectomy

Risk factors for severe sepsis/septic shock of any cause that occurred during prospective follow-up were analyzed using a Cox proportional hazards model (Table 4). Of the variables included in the model, only a Charlson comorbidity index score of 2–3 or >3 was independently associated with the outcome (hazard ratio, 4.2 and 5.8, respectively). When severe sepsis/septic shock due to *S. pneumoniae* or sepsis of unknown etiology was used as the outcome, similar results were obtained (Supplementary Table 1).

Mortality After Splenectomy

During the follow-up period, a total of 90 (20%) study participants died after a median time (IQR) of 1.5 (0.9–3.1) years (range, 0.2 to 6.5 years). After a review of medical records, the cause of death was classified as infection-related in 9 patients (10%); in 53 patients (59%), death was deemed to be related to underlying comorbid illness. Other causes of death or an unknown cause of death accounted for the remaining 28 deaths (32%).

Table 1. Baseline Characteristics of Study Patients

Characteristic	All Patients (n = 459)		Early Study Entry (n = 268)		Delayed Study Entry (n = 191)		*P* Value[a]
	No.	%	No.	%	No.	%	
Age group, y							.086
<15	5	1	2	1	3	2	
15–29	42	9	22	8	20	10	
30–59	211	46	113	42	98	51	
≥60	201	44	130	49	71	37	
Male gender	246	54	152	57	94	49	.112
Underlying risk factors for pneumococcal disease[b]							.019
No additional risk	193	42	98	37	95	50	
At risk	57	12	36	13	21	11	
High risk	209	46	134	50	75	39	
Charlson comorbidity index, median							.002
<2	211	46	105	39	106	55	
2–3	135	29	86	32	49	26	
>3	113	25	77	29	36	19	
Immunosuppressive and/or antineoplastic therapy	97	21	62	23	35	18	.258
Median time from splenectomy to study entry, d	64	—	37	—	1407	—	<.001
Reason for asplenia							<.001
Underlying malignancy	187	41	126	47	61	32	
Trauma	99	22	52	19	47	25	
Therapeutic splenectomy	63	14	27	10	36	19	
Benign abdominal process	48	10	35	13	13	7	
Functional hyposplenia or asplenia	10	2	0	0	10	5	
Other	36	8	20	7	16	8	
Unknown	16	3	8	3	8	4	

[a]Early vs delayed study entry, chi-square test or Fisher exact test, as appropriate.

[b]Risk factors other than splenectomy/asplenia according to the German Standing Committee for Immunization (STIKO) [5]. At-risk factors according to STIKO include chronic diseases of the cardiovascular system or respiratory tract, metabolic diseases (eg, diabetes mellitus treated with oral medication or insulin), and neurological diseases (eg, cerebral palsy, seizure disorders). High-risk conditions according to STIKO include congenital or acquired immunodeficiencies or immunosuppression, such as T-cell deficiency or defective T-cell function, B-cell or antibody deficiency, deficiency or dysfunction of myeloid cells, complement and properdin deficiencies, neoplastic diseases, HIV infection after bone marrow transplantation, immunosuppressive therapy, immunodeficiency in the context of chronic kidney failure, nephrotic syndrome, or chronic liver insufficiency.

DISCUSSION

This is the first prospective cohort study of patients with anatomical or functional asplenia to include individual patient-level follow-up. In the context of a dedicated outpatient service, a high cumulative uptake for pneumococcal, meningococcal, and HiB vaccination could be achieved. As compared with patients with delayed study entry, pneumococcal vaccine uptake within 3 months after splenectomy was almost 3 times higher in patients who had entered the study soon after splenectomy. Over a median prospective follow-up of 2.9 years, we observed a high incidence rate of severe sepsis/septic shock. During the retrospective observation period before study entry, 36% of episodes of postsplenectomy sepsis were caused by *S. pneumoniae*, whereas only 1 episode of pneumococcal sepsis was documented in splenectomized patients after study entry (yielding an estimated incidence of pneumococcal sepsis of <1 per 1000 patient years after study entry).

In the context of splenectomy surveillance linked to referral to an outpatient service, a cumulative uptake of 90% for pneumococcal vaccination was achieved in our study population. Among patients who had undergone dedicated care immediately following surgery, the proportion who received early pneumococcal vaccination within 3 months of splenectomy was 71%. By contrast, for patients who entered the study late after splenectomy, pneumococcal vaccine coverage was only 27% for the respective time period. Dedicated postsplenectomy care also improved early uptake for meningococcal and HiB vaccination. Coverage for pneumococcal vaccination in our cohort compares favorably to overall pneumococcal vaccination rates of only 5% within 2 years after first documentation of a high-risk condition in German adults [15]. Lau assessed the efficacy of quality improvement interventions for increasing the rates of influenza and pneumococcal vaccinations among community-dwelling adults in a systematic review and meta-analysis [16]. In their analysis, team change, patient outreach, and clinician reminders were effective in improving pneumococcal vaccination uptake. Our study, which used a combination of these interventions,

Table 2. Vaccination Within 3 Months Postsplenectomy in Patients With Early and Delayed Study Entry

Vaccine	Early Study Entry[d] (n = 268)		Delayed Study Entry[d] (n = 191)		*P* Value[a]
	No.	%	No.	%	
Pneumococcal vaccination[b]	189	71	51	27	<.0001
Meningococcal vaccination[c]	139	52	32	17	<.0001
HiB conjugate vaccine	186	69	34	18	<.0001
Fully vaccinated[e]	119	44	17	9	<.0001

Abbreviation: HiB, *Haemophilus influenzae* type B.

[a]Fisher exact test.

[b]Defined as vaccinated with at least 1 dose of a pneumococcal vaccine licensed in adults (ie, 23-valent pneumococcal polysaccharide vaccine or 13-valent pneumococcal conjugate vaccine).

[c]Defined as vaccinated with at least 1 dose of meningococcal vaccine (ie, quadrivalent meningococcal polysaccharide vaccine, monovalent or quadrivalent meningococcal conjugate vaccine, or meningococcal serogroup B vaccine).

[d]Delayed study entry was defined as entry >3 months postsplenectomy; early study entry was defined as entry ≤3 months after splenectomy (including the period before splenectomy).

[e]Vaccinated against pneumococcal and meningococcal disease as well as *H. influenzae* type B infection.

confirms the findings by Lau. Significant improvement in vaccination coverage among asplenic patients has also been reported for the use of automated referral letters to vaccination clinics and computer-aided vaccination alerts [17, 18].

During prospective follow-up, we observed high incidence rates both for infections leading to hospitalization and for severe sepsis and septic shock. Other cohort studies of splenectomized patients reported a lower incidence of hospitalization for infection and/or severe sepsis/septic shock, but these were based on either passive surveillance or retrospective analysis [6, 19, 20]. Active, patient-level follow-up likely minimized underascertainment in our study. The inclusion of postoperative periods with health care–associated infections in the study's follow-up time may have further contributed to the higher incidence rate. As with other studies, all-cause mortality after splenectomy in our cohort was high [7], but only 10% of deaths were considered infection-related.

For sepsis episodes that occurred after study entry, the etiology of microbiologically confirmed cases largely resembled the pathogen pattern of the general sepsis population. By contrast, 36% (8/22) of postsplenectomy sepsis episodes that occurred in patients before study entry were due to pneumococci. Of note, 7 of 8 patients with pneumococcal sepsis in this group had not received a pneumococcal vaccine. Similarly high proportions of pneumococcal postsplenectomy sepsis were reported in the Australian registry (32%), in a prospective OPSI cohort study from Germany (59%), and in a retrospective cohort from Minnesota (47%) [2, 7, 19]. In a retrospective, population-based cohort study in Denmark, by contrast, bacteremia episodes caused by pneumococcus were rare [20].

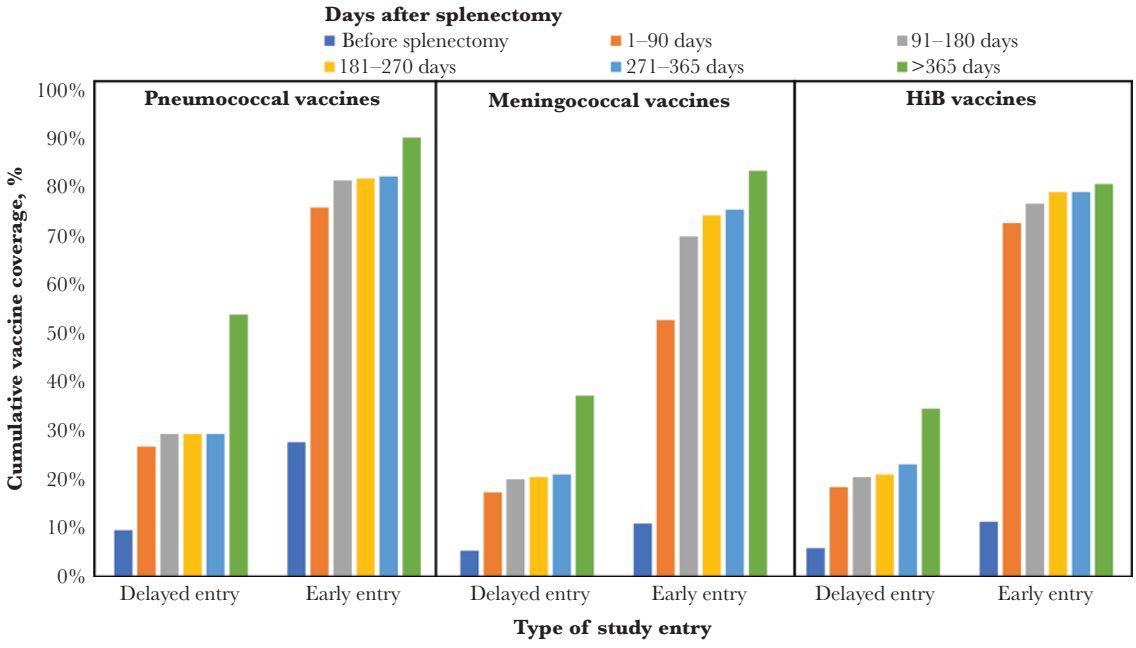

Figure 2. Cumulative vaccine coverage in patients with splenectomy for pneumococcal, meningococcal, and *Haemophilus influenzae* type B (HiB) vaccination. Patients who entered the study >3 months after splenectomy were considered "delayed study entry" (n = 191), whereas patients who entered the study within 3 months of splenectomy were considered "early study entry" (n = 268). Pneumococcal vaccination status was defined as the receipt of least 1 dose of the 23-valent pneumococcal polysaccharide vaccine (PPV23) or the 13-valent pneumococcal conjugate vaccine (PCV13) for pneumococcal vaccination. Meningococcal vaccination status was defined by receipt of at least 1 dose of the quadrivalent meningocoocal polysaccharide vaccine (MPSV4), a mono- or quadrivalent meningococcal conjugate vaccine (MenC or MenACWY), or a meningococcal serogroup B vaccine (MenB) for meningococcal vaccination.

The substantial differences in sepsis etiology in our cohort before and after study entry are remarkable but in part may be explained by various sources of bias, such as differential case ascertainment, patient recall bias, or study inclusion bias.

Recent evidence for the protective role of pneumococcal vaccination comes from the Australian splenectomy register and the retrospective Olmstead County splenectomy cohort (USA) [7, 21]. In the present study, only comorbidity had a measurable impact on the risk of severe sepsis/septic shock—not the receipt of a pneumococcal vaccine. However, our analysis was limited by several factors. Vaccine protection for both pneumococcal vaccines licensed for use in adults is imperfect and requires large sample sizes to demonstrate effectiveness [22–24]. Also, our study was likely underpowered for the purpose of demonstrating the impact of pneumococcal vaccination on severe sepsis or septic shock. However, even after all limitations of comparisons between prospective and retrospective data are considered, the substantially lower proportion of pneumococcal sepsis in patients who had undergone systematic pneumococcal vaccination by our dedicated outpatient clinic remains intriguing.

Our study's strengths include its prospective design with active, patient-level follow-up. Vaccination status and infection diagnosis were validated by reviewing hospital documentation and discharge records. Plausibility checks by trained infectious diseases specialists are likely to have led to fewer misclassifications than in studies that use only health claims data [25]. The limitations of our study include the relatively small cohort size as compared with retrospective cohorts, the significant proportion of patients lost to follow-up, and the relatively short follow-up period. Loss to follow-up may have led to either overestimation or underestimation of true vaccination rates. As with other cohort studies, reliance on standard-of-care diagnostics likely has led to an underdiagnosis of pneumococcal sepsis [26]. Furthermore, a significant proportion of subjects were at risk before study entry, and some episodes of severe sepsis/septic shock occurred before the patients' entry into the cohort—factors that impact the comparability of these retrospectively captured episodes. We therefore reported infection incidence only for the period of prospective follow-up. Because of the different durations of the retrospective and prospective observation periods, absolute numbers of sepsis episodes were not

Table 3. Episodes of Infections Requiring Hospitalization After Splenectomy, With Data Stratified by Patients who Met the Criteria for Severe Sepsis or Septic Shock

	Infection Episodes After Study Entry						Infection Episodes Before Study Entry	
	Total (n = 164)		No Severe Sepsis/ Septic Shock (n = 142)		Severe Sepsis/ Septic Shock (n = 22)		Severe Sepsis/ Spetic Shock (n = 22)	
Characteristics	No.	%	No.	%	No.	%	No.	%
Site of infection								
Lower respiratory tract	33	20	26	18	7	32	4	18
Central nervous system	0	0	0	0	0	0	3	14
Intra-abdominal	26	16	22	15	4	18	2	9
Bones and soft tissue	19	12	18	13	1	5	1	5
Surgical wound infection	9	6	9	6	0	0	0	0
Urinary tract infection	14	9	9	6	5	23	0	0
Primary bacteremia	11	7	10	7	1	5	7	32
Central line infection	10	6	9	6	1	5	1	5
Other	31	19	31	22	0	0	4	18
Unknown	19	12	16	11	3	14	0	0
Pathogen isolated								
Staphylococcus aureus	14	9	13	9	1	5	0	0
Coagulase-negative staphylococci	5	3	5	4	0	0	0	0
Streptococcus pneumoniae	1	1	0	0	1	5	8	36
Other gram-positives	9	6	9	6	0	0	1	5
Escherichia coli	16	10	7	5	9	41	1	5
Klebsiella spp.	5	3	3	2	2	9	0	0
Other gram-negatives	4	2	4	3	0	0	1	5
Anaerobes	1	1	1	1	0	0	0	0
Polymicrobial infection	7	4	7	5	0	0	0	0
Fungal infection	3	2	3	2	0	0	1	5
Viral infection	7	4	7	5	0	0	0	0
No pathogen detected	99	56	83	58	9	41	10	45

Table 4. Risk Factors for Prospectively Captured First Episodes of Severe Sepsis/Septic Shock From any Cause in Asplenic Patients

Variable		PYO	Episodes of Sepsis/ Septic Shock	Multivariate Hazard Ratio (95% Confidence Interval)[a]	*P* Value[b]
Sex	Male	810	13	Reference	.29
	Female	647	6	0.59 (0.21–1.59)	
Age	<60 y	897	8	Reference	.65
	>60 y	560	11	1.26 (0.47–3.39)	
Charlson score at baseline visit	<2	762	4	Reference	.04
	2–3	395	8	4.14 (1.09–15.74)	
	>3	300	7	5.79 (1.39–24.02)	
Indication for splenectomy	Trauma	284	2	Reference	.22
	Solid tumor	418	5	0.38 (0.06–2.43)	
	other	755	12	1.01 (0.20–5.10)	
Time since splenectomy at baseline visit	≤12 mo	932	14	Reference	.48
	>12 mo	514	5	0.68 (0.21–2.23)	
Pneumococcal vaccination before sepsis	Not vaccinated	137	3	Reference	.60
	≥1 vaccine dose	1320	16	0.61 (0.16–2.27)	
Immunosuppression incl. chemotherapy at baseline visit	No	1157	14	Reference	.39
	Any	300	5	1.72 (0.65–4.54)	

Abbreviation: PYO, patient-years of observation.

[a]Cox regression (No. of subjects, 426; events, 19; time at risk, 1445 patient-years).

[b]Likelihood ratio test.

directly comparable. Furthermore, we did not collect information on the number of patients who were eligible for the study but declined study participation. In addition, because this was a single-center study, we were unable to exclude center effects that may have impacted the study, including patient mix, hospital admission policies for infections, and standard-of-care microbiological diagnostics.

In summary, our study demonstrates that postsplenectomy, patients are at high risk for severe sepsis/septic shock. However, hospital-based surveillance of splenectomies, combined with referrals to dedicated outpatient services, can improve the implementation of infection prevention measures, including vaccination uptake—which makes pneumococcal sepsis a rare complication.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. S.R. supervised the data acquisition and validation and contributed to the interpretation of the data and to the writing of the manuscript. L.B., K.N., J.H., M.F.J.K., K.S., M.C.M., and I.J. contributed to the data acquisition. B.L. contributed to the data acquisition and performed the statistical analysis. W.V.K. contributed to the data interpretation and to the writing of the manuscript. C.T. conceived the study, contributed to the data acquisition, validation, and statistical analysis, and wrote the manuscript.

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