



Vaccination and splenectomy in Olmsted County

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ABSTRACT

Objectives: To determine the long-term impact of vaccination on any postoperative infection in adults who underwent splenectomy.

Methods: All adults (≥ 18 years) who underwent splenectomy from 1965 to 2011 in Olmsted County, MN were identified using the Rochester Epidemiology Project. Descriptive statistics, Kaplan-Meier estimates, and Cox proportional hazard ratios were performed.

Results: There were 724 patients who underwent splenectomy; 47% were female with a median age of 55 (35–69) years. Overall vaccination rate (pneumococcal, *H influenza*, meningococcal) was 62% ($n = 449$). There were 268 (36%) patients who developed a post-splenectomy infection; most presented with sepsis 148 (55%). The 3 most common infections included pneumonia (124, 17%), bloodstream (67, 9%), and urinary tract infection (49, 7%). Median time to infection was quicker in non-vaccinated compared with vaccinated patients (1.5 [0.1–4.3] vs 3.3 [1.9–9.8] years, $P = .01$).

Conclusion: In this population-based study, the highest risk of infection after splenectomy was in patients who did not receive complete vaccination. Lack of complete vaccination was associated with a reduced time to infection and increased rates of bloodstream infections at 5 years. Infectious complication risk reduced as vaccination protocols improved for all indications except for malignancy. Adults who underwent a splenectomy should continue to receive booster vaccines.

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Introduction

The spleen provides immunologic and hematopoietic function and has a pulverulent texture, which receives considerable cardiac output.¹ Asplenia can result in loss of adaptive immunity and alterations in several serum immunologic factors, which can increase the risk of infection.^{2–4} Morris and Bullock demonstrated this vulnerability⁵ that was rendered more conclusive by King and Schumacker in their description of overwhelming post-splenectomy infection (OPSI) in children and its high mortality.⁶ As a result of the increased susceptibility to encapsulated organism infection from asplenia, notably pneumococcus, meningococcus, and *Haemophilus influenzae* b (Hib), preventative measures like vaccination may lower the risk of post-splenectomy infection.

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Owing to the need for large populations to determine the correlation between immunizations and the risk of long-term post-splenectomy infections, we used the Rochester Epidemiology Project (REP), an exclusive epidemiologic project that compiles medical record data for all Olmsted County residents and allows for accurate identification and tracking of health care. We have previously used the REP to determine the rates of postsplenectomy sepsis in children because the spleen plays a critical role in antibody response to polysaccharide antigens contained on bacterial cell wall during childhood. This role is more mature in adult patients, making the role of vaccinations in the long term less clear.⁷ Therefore, the REP was used to enumerate in adult patients the long-term incidence and outcomes of postsplenectomy infection residing in Olmsted County, Minnesota.

Methods

Cohort

Within Olmsted County, at both Mayo Clinic and Olmsted Medical Center, institutional review board approval was obtained.

Within southeastern Minnesota, Olmsted County is remote from other medical centers and this permitted study of the long-term outcomes after splenectomy. Based on results that evaluated the natural course after splenectomy in children,⁷ the REP was used to perform a similar study in adults. Briefly, the REP maintains pooled patient-specific medical record data for consented community members for epidemiologic and historical cohort research. Data specialists continuously update the population-based project through classification of historical patient data.⁸ Beginning in 1965, the REP encompasses medical treatment for most citizens within Olmsted County.⁹ The REP is able to unify patient identification with the complete medical record for patients who underwent care at either institution. Patient care is codified and routinely updated. These include outpatient and inpatient visits. Data maintained within the REP accurately follow the care for most Olmsted County residents.¹⁰ When patients die or leave Olmsted County and no longer receive care by a participating REP provider, these were considered as data attrition. Despite this, individuals who have migrated out of Olmsted County are tracked using patient identifiers when consulting with another health care provider. Further, when patients continue to receive care at centers that participate within the REP, these data are maintained and updated within the REP database. The highest rates of attrition are in those aged 15 to 26 years.¹⁰ Recent data assessing the integrity of the REP demonstrated that about 20% of the entire population has undergone attrition.¹⁰

Using diagnosis and procedure codes, Olmsted County residents who underwent splenectomy were identified using procedural codes. These codes included *International Classification of Diseases, Ninth Edition* code 41.5 (total splenectomy) or *Current Procedural Terminology* codes (38100 excision procedures on the spleen; 38102 total excision of the spleen, in conjunction with another procedure; 38120 laparoscopic procedures on the spleen). Receipt of vaccine of the following encapsulated organisms (*S pneumoniae*, *H influenzae*, and *N meningitidis*) was obtained. All patients were followed until death, migration from Olmsted county, or last follow-up. REDCap electronic software hosted at the study institution were used to maintain the database.¹¹

Definitions

In patients with asplenia, the phenomenon of OPSI can occur. After infection with encapsulated bacteria, rapid and fulminant progression of the infection is considered OPSI. In patients who underwent splenectomy, the hospital charts were reviewed for infections including pneumonia, urinary tract infection, acute otitis media, meningitis, nonsurgical abscess, bloodstream infection, or peritonitis. Among those with an infection, the severity of the infection was assigned and culture data were assessed to identify the infectious vector. Infection severity was graded based previously described sepsis definitions.¹² OPSI-related death was due to infection with encapsulated bacteria during hospitalization.

Data analysis

To estimate survival, the Kaplan-Meier method was used. Both survival free of infection and survival free of OPSI were calculated. A competing risks approach was used. This was used to justify the risk of death in patients without infection. To determine associations with duration to any infection or OPSI, Cox proportional hazards regression was used and expressed as hazard ratios (HRs) and 95% confidence intervals [CIs]. These were stratified by year of surgery to adjust for practice changes and outcomes throughout the study period. Associations with the cumulative incidence of infection after accounting for the competing risk of death without

infection were evaluated using the proportional sub-distribution model.¹³ To calculate incidence rates, the number of incident cases was considered the numerator and age- and sex-specific Olmsted County population counts were the denominators. The denominators were obtained from a complete enumeration of the Olmsted County population provided by the REP.¹⁴ Because Olmsted County contains a predominantly white population, incidence rates were directly age- and sex-adjusted to the structure of the 2010 US white population. Using SAS procedure GENMOD, relationships were assessed with incidence rates by fitting Poisson regression models for the variables of age, sex, and timing of splenectomy. Statistical analyses were performed using version 9.3 of the SAS software package (SAS Institute, Cary, NC). All tests were 2-sided and *P* values <.05 were considered statistically significant.

Results

There were 724 patients who underwent splenectomy. Among these, 709 patients (97%) were from Mayo Clinic and 15 patients (3%) were from Olmsted Medical Center. Forty-seven percent were female and the median cohort age was 55 (35–69) years. The features collected for the 724 adult patients are summarized in [Table 1](#). At last follow-up, 429 patients had died at a median of 2.6 years

Table 1
Summary of features for adult patients, N = 724

Feature	Median (IQR; range)
Age at surgery in years	55 (34.5–69; 18–102)
Sex	N (%)
Female	340 (47)
Male	384 (53)
Year of surgery	
1966–1969	39 (5)
1970–1974	85 (12)
1975–1979	114 (16)
1980–1984	91 (13)
1985–1989	70 (10)
1990–1994	68 (9)
1995–1999	62 (90)
2000–2004	82 (11)
2005–2009	75 (10)
2010–2011	38 (5)
Indication for splenectomy	
Trauma	139 (19)
Malignancy	256 (35)
Benign hematologic disease	83 (11)
Intraoperative iatrogenic injury	90 (12)
Other	156 (22)
Type of malignancy (N = 256)	
Hodgkin's lymphoma	51 (20)
Non-Hodgkin's lymphoma	30 (12)
Hairy cell leukemia	11 (4)
Chronic lymphocytic leukemia	17 (7)
Chronic myelogenous leukemia	3 (1)
Non-hematologic tumor of the spleen	3 (1)
Other	141 (55)
Type of hematologic disease (N = 83)	
Idiopathic thrombocytopenic purpura	55 (66)
Spherocytosis	6 (7)
Hemolytic anemia	16 (19)
Other	6 (7)
Type of splenectomy	
Elective	509 (70)
Emergent	215 (30)
Technical approach	
Open	666 (92)
Laparoscopic converted to open	17 (2)
Laparoscopic	41 (6)
Pancreatectomy performed	48 (7)
Gastrectomy performed	48 (7)
Other procedure performed	332 (46)

after surgery (interquartile range [IQR] 0.5–11.0; range 0 days to 40.3 years). Among the 295 patients alive at last follow-up, the median duration of follow-up was 11.1 years (IQR 4.4–25.9; range 9 days to 46.6 years). The 724 adult patients in the study contributed a total of 7,653 person-years of follow-up.

Overall, the age- and sex-adjusted incidence of splenectomy was 23.3 per 100,000 person-years. Incidence rates by age at splenectomy are illustrated in Fig 1. For all age groups, incidence rates were higher for men than for women, particularly for ages 18 to 29 ($P = .004$) and for ages 60 and older ($P < .001$). For both men and women, incidence rates increased significantly with age ($P < .001$ for both). Incidence rates by year of splenectomy are illustrated in Fig 1. For women, incidence rates decreased over time ($P = .011$). For men, incidence rates increased between 1966 and 1979 ($P < .001$), decreased until 1994 ($P < .001$), and then remained fairly constant ($P = .88$).

In those who were traumatically injured, incidence rates of splenectomy peaked in 1975 to 1979 but were relatively constant thereafter (Fig 1). For cases of malignancy, incidence rates of splenectomy increased between 1966 and 1979, steadied, and then decreased through the end of the study period ($P = .009$). Incidence rates of splenectomy for benign hematologic diseases did not change significantly over time. Incidence rates of splenectomy for intraoperative iatrogenic injury peaked in 1970 to 1974, decreased until 1989, and then remained constant. Similarly, incidence rates of splenectomy for other indications peaked in 1970 to 1974, decreased until 1989, and then remained fairly constant.

Most patients underwent an open splenectomy (666, 92%), 41 underwent laparoscopy (6%), and 17 underwent laparoscopy converted to an open procedure (2%). Most patients underwent elective splenectomy (509, 70%) compared with an emergency (215, 30%) (Table 1). During the procedure, most patients underwent only splenectomy (312, 42%) whereas 48 patients underwent splenectomy and pancreatectomy (7%), 48 patients underwent splenectomy and gastrectomy (7%), and 316 patients underwent splenectomy with another concomitant procedure (44%).

After splenectomy, the overall vaccination rate during the entire study period (receipt of all 3 vaccines: pneumococcal, meningococcal, and Hib) was 62% ($n = 449$). During the study period, receipt of all 3 vaccines improved each decade (Fig 2). Complete vaccination rates were highest in contemporary patients wherein the final decade approached vaccination rates of nearly 100%. Booster vaccines were administered to 232 patients (32%), and the type administered varied. Among the patients who received booster vaccines, the rate for each vaccine type was (30.8%) for streptococcal, (4.4%) for meningococcal, and (1.9%) for Hib. Booster vaccines were administered at a median of 8 (interquartile range 5–18) months since the time of splenectomy. The complete (receipt of all 3 booster vaccines) booster vaccination rate was 0.8%. Multivariable associations with infectious-related mortality included age >65 years (HR 2.1, 1.7–2.6), malignant disease (HR 2.7, 1.9–3.8), emergency splenectomy (HR 1.3, 1.1–1.7), not receiving all 3 vaccines (HR 1.7, 1.4–1.9), and no receipt of booster vaccine (HR 1.9, 1.6–2.4) but not male sex (HR 1.2, 0.8–1.4) or open technique (HR 1.1, 0.7–1.4).

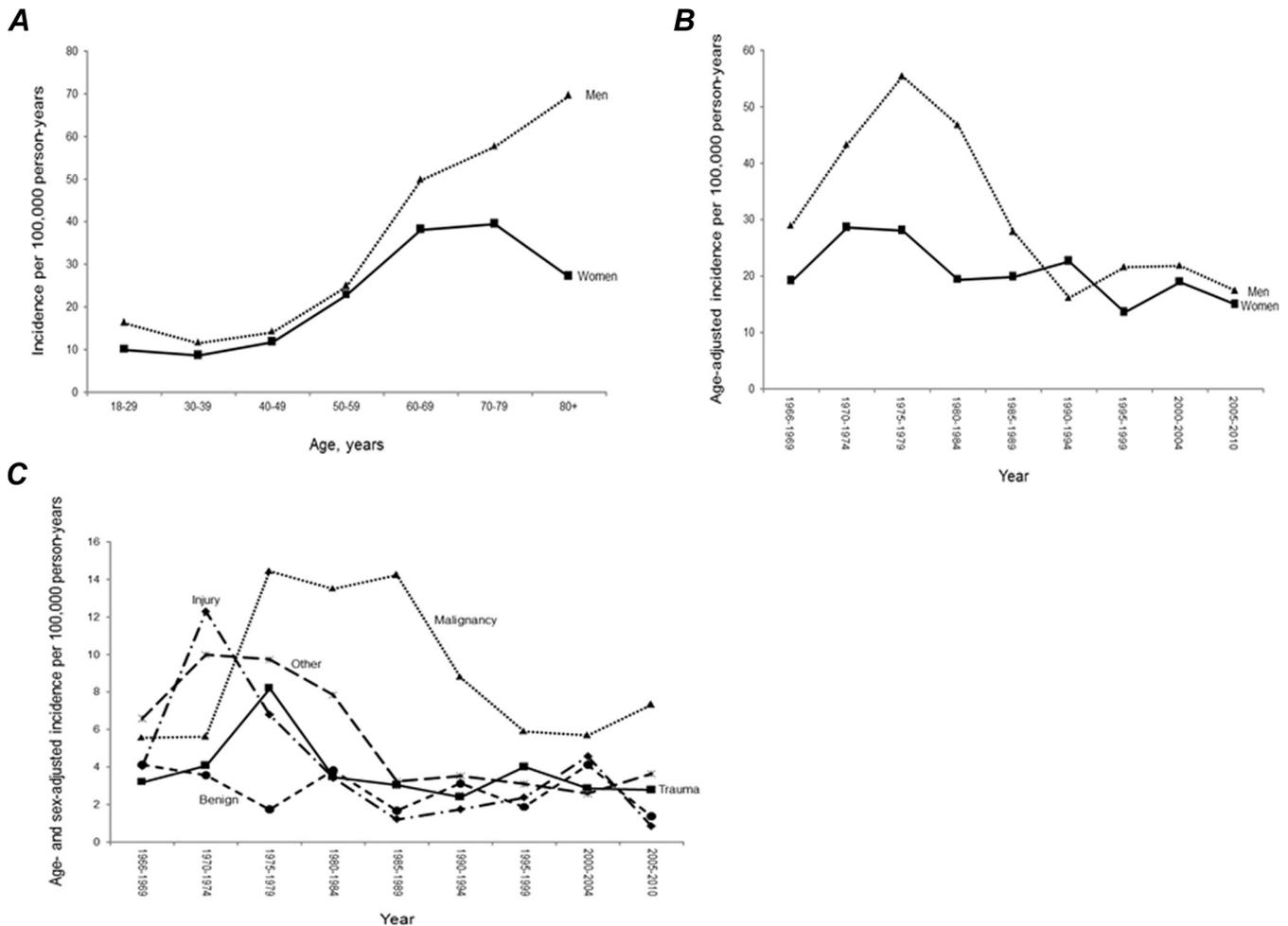


Fig 1. Incidence rates of splenectomy by (A) age, (B) year, and (C) indication.

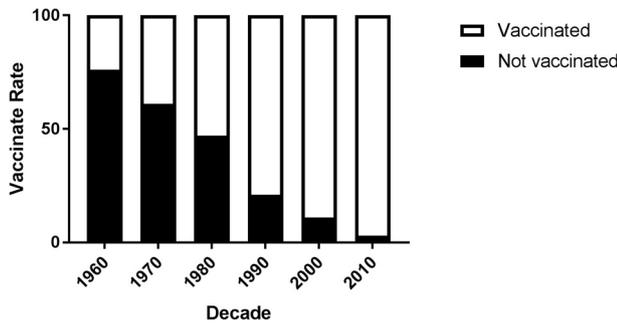


Fig 2. Improvement of receipt of all 3 vaccines each decade.

At last follow-up, 268 patients developed infection. After splenectomy, this occurred at a median of 2.0 years (IQR 0.3–9.1 years; range 0 days to 40.3 years), including 3 patients who developed infection on the same day as the surgery. Most presented with sepsis 148 (55%). The most common infections were pneumonia (124, 17%), bloodstream (67, 9%), and urinary tract infection (49, 7%). Median time to infection was quicker in non-vaccinated compared with vaccinated patients (1.5 [0.1–4.3] vs 3.3 [1.9–9.8] years, $P = .01$). In patients with postsplenectomy infection, 74 (27%) died; of these, 52 (70%) were due to the infection. These patients died predominantly from sepsis, and among these, 32 died owing to OPSI. The median duration of follow-up for the 456 patients who did not develop infection was 4.9 years (IQR 1.0–15.8 years; range 0 days to 46.6 years); there were 13 patients who died on the same day as surgery. Features of the 268 patients with infection are summarized in Tables II and III.

After splenectomy, the estimated rates of survival free of infection and survival free of infection with competing risk of death are presented in Table IV. This accounted for competing risks of death without infection. Associations with duration to infection are summarized in Table V. The multivariable model that accounted for competing risk of death without infection was evaluated and the results were similar, although the HRs for age, sex, and indication for splenectomy were somewhat attenuated. The HR for the

Table II
Summary of adult patients with infection of any type, N = 268

Feature	N (%)
Number of admissions for infection (N = 267)	
1	166 (62)
2	55 (21)
3	31 (12)
4	8 (3)
5	4 (2)
7	1 (<1)
9	1 (<1)
10	1 (<1)
Type of infection	
Pneumonia	124 (46)
Urinary tract infection	49 (18)
Otitis media	1 (<1)
Superficial surgical site infection	8 (3)
Deep surgical site infection	26 (10)
Meningitis	8 (3)
Abscess (nonsurgical site)	14 (5)
Peritonitis	4 (1)
Bloodstream	67 (25)
Other	31 (12)
Severity of infection (N = 194)	
Sepsis	140 (72)
Severe sepsis	37 (19)
Septic shock	17 (9)

Table III
Summary of infection-related outcomes and organisms

Culture available	208 (78)
Type of culture available (N = 208)*	
Blood	128 (62)
Secretion	56 (27)
Tissue	31 (15)
Other	60 (29)
Organism (N = 186)*	
<i>E coli</i>	32 (17)
<i>Pseudomonas aeruginosa</i>	25 (13)
<i>Staphylococcus aureus</i>	24 (13)
<i>Streptococcus pneumonia</i>	16 (9)
<i>Enterobacter</i>	13 (7)
<i>Klebsiella pneumonia</i>	13 (7)
<i>Enterococcus</i>	11 (6)
<i>Staphylococcus epidermidis</i>	11 (6)
<i>Candida albicans</i>	10 (5)
No growth	10 (5)
<i>Streptococcus viridans</i>	8 (4)
Group B streptococcus	6 (3)
<i>Bacteroides fragilis</i>	5 (3)
Group D streptococcus	5 (3)
Mixed flora	4 (2)
<i>Proteus</i>	4 (2)
<i>Clostridium difficile</i>	3 (2)
<i>Aspergillus</i>	3 (2)
<i>Hemophilus</i>	3 (2)
<i>Meningococcus</i>	2 (1)
<i>Serratia</i>	2 (1)
Yeast	1 (1)
<i>Aeromonas</i>	1 (1)
<i>Bacillus cereus</i>	1 (1)
CMV	1 (1)
<i>Candida krusei</i>	1 (1)
<i>Citrobacter</i>	1 (1)
<i>Cryptococcus</i>	1 (1)
Group A streptococcus	1 (1)
Group G streptococcus	1 (1)
<i>Klebsiella oxytoca</i>	1 (1)
<i>Listeria monocytogenes</i>	1 (1)
<i>Mycobacterium kansasii</i>	1 (1)
PCP	1 (1)
<i>Salmonella typhi</i>	1 (1)
<i>Stenotrophomonas maltophilia</i>	1 (1)
<i>Streptococcus agalactiae</i>	1 (1)
<i>Enterobacter cloacea</i>	1 (1)
<i>Aspergillus fumigatus</i>	1 (1)
<i>Klebsiella oxytoca</i>	1 (1)
<i>Peptostreptococcus</i>	1 (1)
Multiple organisms on culture (N = 186)	48 (26)
OPSI (N = 186)	32 (17)
In-hospital death	74 (28)
In-hospital death from sepsis	52 (19)

CMV, cytomegalovirus; PCP, *Pneumocystis pneumonia*.

* Patients can be listed in more than 1 group.

association of age (10-year increase) with the cumulative incidence of infection was 1.17 (95% CI 1.09–1.26; $P < .001$); the HR for male was 1.14 (95% CI 0.89–1.46; $P = .31$); the HRs for the indications of malignancy, benign hematologic disease, intraoperative iatrogenic injury, and any other indication were 1.88 (95% CI 1.06–3.34; $P = .031$), 1.64 (95% CI 0.85–3.18; $P = .14$), 1.24 (95% CI 0.64–2.42; $P = .52$), and 2.16 (95% CI 1.27–3.68; $P = .005$), respectively.

Sixty patients who did not have a culture available and 22 patients with a culture but no record of a specific organism were excluded from the assessment of survival free of OPSI. At last follow-up, 32 of the remaining 642 patients developed OPSI at a median of 2.4 years after surgery (IQR 0.2–8.8 years; range 1 day to 31.0 years). Features of the 32 patients with OPSI are summarized in Table VI. After splenectomy, estimated rates of survival free of OPSI and OPSI after accounting for the competing risk of death without OPSI are seen in Table VII. Univariable associations with time to OPSI are summarized in Table VIII. A multivariable model was built

Table IV
Estimated rates of survival free of infection

Time point (year)	Survival free of infection (95% CI; number still at risk)	Survival free of infection with competing risk of death (rate)
1	84% (81–87, 500)	85%
2	79% (76–82, 433)	81%
3	76% (73–80, 395)	79%
4	74% (71–78, 356)	78%
5	73% (69–76, 329)	76%
10	62% (58–66, 222)	69%
15	56% (51–61, 159)	65%
20	52% (47–57, 122)	62%

using stepwise selection with the *P* value for a feature to enter or leave the model set to .05. After adjusting for age, no other feature was statistically significantly associated with time to OPSI in a multivariable setting. However, after accounting for the competing risk of death without OPSI, the association of age with the cumulative incidence of OPSI no longer reached statistical significance (hazard ratio for a 10-year increase of 1.14; 95% CI 0.96–1.35; *P* = .14).

Discussion

The main finding in this population-based study is that after splenectomy, a considerable ongoing risk of infectious morbidity and mortality continues to exist. The incidence of splenectomy varied between men and women and the indications changed over time. The most common infection was pneumonia, and *Escherichia coli* was identified in 17% of cultures. Age, malignant diagnosis, and male sex were strong predictors in time to infection, and in those patients who died from infection, increasing age, malignant disease, and lack of receipt of complete vaccination or booster were associated. Vaccination rates improved with time, and the overall rate of complete recommend vaccines was 62%, similar to prior studies.^{15–17} Nearly all patients who underwent splenectomy in the last 2 decades received complete vaccination. Despite the high rates of vaccination toward the end of the study period, only 32% received some form of booster vaccine, which represents a moderate rate of booster vaccination.^{18,19} Finally, the overall OPSI rate

was 4.4%, which is representative of the infrequency of this phenomenon.

In the present study, patients with the highest risk of infection after splenectomy were those with malignant diagnoses. Over a similar time frame, Edgren et al determined that risk of hospital admission for sepsis was nearly 6-fold higher in patients who underwent splenectomy compared with the background population and that indication for splenectomy affected this outcome.²⁰ Edgren's study showed that rates of sepsis varied after splenectomy specifically for malignant and nonmalignant hematologic disease. Edgren et al also demonstrated that in patients with malignant or benign hematologic diseases, the time to infection was quicker, suggesting that this population may require heightened surveillance.²⁰ The mechanism is unclear but may be due to vaccine failure with underlying hematologic disorders.

Vaccination after splenectomy affects patient outcomes. Ejstrud reported on a predominantly adult population with a vaccination rate of 59% and described bacteremia in 40 adults, with nearly half occurring less than 30 days postoperatively.²¹ The authors also found that vaccinated patients have a reduced risk of late (>30 days) bacteremia. In the present study, the overall vaccination rate was similar and in patients who were not vaccinated, the time to infection was quicker in comparison to patients who were vaccinated. Further, no receipt of vaccination or booster vaccination was associated with an increased risk of mortality due to infection on regression. Moreover, the present study had a similar preponderance of infection due to enteric gram-negative rods, meaning that vaccination was effective at reducing encapsulated organism

Table V
Univariable and multivariable associations with time to infection for adult patients

Feature	Univariable		Multivariable	
	Hazard Ratio (95% CI)	<i>P</i> value	Hazard Ratio (95% CI)	<i>P</i> value
Age at surgery in years*	1.45 (1.35–1.56)	<.001	1.43 (1.32–1.55)	<.001
Sex				
Female	1.0 (reference)	.24	1.0 (reference)	.029
Male	1.16 (0.91–1.48)		1.33 (1.03–1.71)	
Indication for splenectomy				
Trauma	1.0 (reference)	<.001	1.0 (reference)	.009
Malignancy	3.42 (2.21–5.29)	.002	2.20 (1.23–4.02)	.062
Benign hematologic disease	2.34 (1.39–3.94)	<.001	1.90 (0.97–3.71)	.20
Intraoperative iatrogenic injury	3.26 (1.92–5.55)	<.001	1.51 (0.80–2.87)	.005
Other	2.81 (1.80–4.38)		2.19 (1.27–3.76)	
Type of splenectomy				
Elective	1.0 (reference)	<.001	1.0 (reference)	.96
Emergent	0.58 (0.44–0.79)		0.99 (0.66–1.49)	
Technical approach				
Open	1.0 (reference)	.76	1.0 (reference)	.21
Laparoscopic converted to open	0.86 (0.34–2.17)	.56	0.55 (0.22–1.40)	.25
Laparoscopic	0.84 (0.48–1.49)		0.70 (0.38–1.28)	
Pancreatectomy performed	0.94 (0.57–1.55)	.81	0.83 (0.48–1.42)	.49
Gastrectomy performed	1.92 (1.16–3.16)	.011	1.04 (0.60–1.80)	.90
Other procedure performed	1.24 (0.97–1.59)	.088	1.18 (0.89–1.57)	.24

* Hazard ratio and 95% CI represent a 10-year increase in age.

Table VI
Summary of adult patients with OPSI, N = 32

Feature	N (%)
Number of admissions for infection	
1	15 (47)
2	8 (25)
3	8 (25)
4	1 (3)
Type of infection*	
Pneumonia	20 (63)
Urinary tract infection	6 (19)
Otitis media	0
Superficial surgical site infection	0
Deep surgical site infection	3 (9)
Meningitis	3 (9)
Abscess (nonsurgical site)	2 (6)
Peritonitis	0
Bloodstream	5 (16)
Other	1 (3)
Severity of infection (N = 20)	
Sepsis	13 (65)
Severe sepsis	5 (25)
Septic shock	2 (10)
Type of culture available*	
Blood	15 (47)
Secretion	14 (44)
Tissue	4 (13)
Other	10 (31)
Organism*	
<i>Streptococcus pneumoniae</i>	15 (47)
<i>Klebsiella pneumoniae</i>	12 (38)
<i>Hemophilus</i>	3 (9)
<i>Meningococcus</i>	3 (9)
<i>E coli</i>	2 (6)
<i>Enterococcus</i>	2 (6)
<i>Staphylococcus aureus</i>	2 (6)
<i>Bacteroides fragilis</i>	1 (3)
<i>Candida krusei</i>	1 (3)
<i>Pseudomonas aeruginosa</i>	1 (3)
<i>Staphylococcus epidermidis</i>	1 (3)
<i>Streptococcus viridans</i>	1 (3)
<i>Clostridium difficile</i>	1 (3)
<i>Klebsiella oxytoca</i>	1 (3)
Multiple organisms on culture	12 (38)
In-hospital death	7 (22)
In-hospital death from sepsis	6 (19)

* Patients can be listed in more than 1 group.

infections. These findings suggest the importance of vaccination prophylaxis and underscore the need for up-to-date databases to improve vaccine adherence.

Surgeons and health-care providers need to remain vigilant to identify infection in patients during prolonged follow-up after splenectomy. In a long-term population analysis evaluating the risk of infection and OPSI by Theilacker et al, pneumonia was found to be the most common etiology for OPSI, even at points greater than 2 years.²¹ In the present study, pneumonia was also the most common infection but also bloodstream, urinary tract, and surgical site infections were frequent. Moreover, nearly one-third of

Table VIII
Univariable associations with time to OPSI for adult patients

Feature	Hazard ratio (95% CI)	P value
Age at surgery in years*	1.42 (1.14–1.75)	.001
Sex		
Female	1.0 (reference)	.21
Male	0.63 (0.30–1.29)	
Indication for splenectomy		
Trauma	1.0 (reference)	.043
Malignancy	3.84 (1.05–14.13)	.18
Benign hematologic disease	2.79 (0.62–12.63)	.072
Intraoperative iatrogenic injury	4.05 (0.88–18.58)	.061
Other	3.50 (0.94–13.04)	
Type of splenectomy		
Elective	1.0 (reference)	.24
Emergent	0.61 (0.27–1.38)	
Technical approach†		
Open	1.0 (reference)	.26
Laparoscopic converted to open or laparoscopic	0.31 (0.04–2.41)	
Pancreatectomy performed	0.86 (0.20–3.66)	.84
Gastrectomy performed	1.90 (0.44–8.30)	.39
Other procedure performed	1.08 (0.53–2.21)	.83

* Hazard ratio and 95% CI represent a 10-year increase in age.

† No patient with laparoscopic converted to open experienced OPSI, so laparoscopic converted to open was combined with laparoscopic for analysis.

patient's presented with infection more than once during follow-up, which underscores the need to rule out life-threatening infections in this patient population. Theilacker's findings highlight the importance of the present study's results—patients still are continuously at risk for infection long after splenectomy.²² Not surprisingly, the few instances of OPSI attenuated the ability to determine predictive risk factors; however, efforts to educate patients about persistent infection risk should be provided throughout follow up.

Finally, the Centers for Disease Control recommends a series of vaccinations and boosters in patients with asplenia and or hypoplasia.²³ We recommend the vaccination strategy according to these guidelines. These are comprehensive recommendations but omit recommendations for booster vaccination. Because nearly one-third of patients received a booster *Pneumococcal* vaccine, we recommend this booster to patients who have had a splenectomy. Because most patients did not receive booster vaccines for *Meningococcal* or Hib, we cannot recommend these routinely, especially because a paucity of data exists.

This study has limitations; specifically, those infectious-related outcomes after splenectomy were not compared relative to the background population, meaning that we could not determine whether infection rates were higher in comparison to those who have not undergone splenectomy. Further, there were missing data regarding splenectomy indication. Despite similar rates of vaccination compared with prior studies, the associations of reduced infection rates may be overestimated owing to lack of information regarding the timing of vaccines and the booster. Analysis

Table VII
Estimated rates of survival free of OPSI

Time point (year)	Survival free of OPSI (95% CI; number still at risk)	Survival free of infection with competing risk of death (rate)
1	98% (97–100, 450)	99%
2	97% (95–98, 392)	98%
3	97% (95–98, 355)	97%
4	97% (95–98, 320)	97%
5	96% (94–98, 296)	97%
10	93% (91–96, 206)	95%
15	91% (88–94, 147)	94%
20	90% (87–94, 115)	94%

regarding risk factors for OPSI was not feasible owing to low sample size. The duration of the study period also reflects considerable changes in the administration of health care, anesthesia, intensive care, antibiotic availability, and vaccination availability and efficacy.

In conclusion, our study highlights that after splenectomy, the risk of infection and OPSI persists throughout the 20-year follow-up period. Patients who were not administered vaccines displayed quicker times to infection and infectious-related mortality. Despite efforts to vaccinate against common encapsulated organisms, the most common microorganisms encountered were gram-negative rods. Efforts to improve vaccination surveillance appear to be warranted to minimize infection and mortality risk.

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Conflict of interest/Disclosure

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References

- Sills RH, Kelton JO. Splenic function: physiology and splenic hypofunction. *Crit Rev Oncol Hematol*. 1987;7:1–36.
- Cameron PU, Jones P, Gorniak M, et al. Splenectomy associated changes in IgM memory B cells in an adult spleen registry cohort. *PLoS One*. 2011;6:e23164.
- Amlot PL, Hayes AE. Impaired human antibody response to the thymus-independent antigen, DNP-Ficoll, after splenectomy. Implications for post-splenectomy infections. *Lancet*. 1985;1:1008–1011.
- Lanng Nielsen J, Tauris P, Johnsen HE, Ellegaard J. The cellular immune response after splenectomy in humans. Impaired immunoglobulin synthesis in vitro. *Scand J Haematol*. 1983;31:85–95.

- Morris DH, Bullock FD. The importance of the spleen in resistance to infection. *Ann Surg*. 1919;70:513–521.
- Bisharat N, Omari H, Lavi I, Raz R. Risk of infection and death among post-splenectomy patients. *SOJ Infect*. 2001;43:182–186.
- King H, Shumacker HB Jr. Susceptibility to infection after splenectomy performed in infancy. *Ann Surg*. 1952;136:239–242.
- Khasawneh MA, Contreras-Peraza N, Hernandez MC, Lohse C, Jenkins DH, Zielinski MD. Outcomes after splenectomy in children: a 48-year population-based study. *Pediatr Surg Int*. 2019;35:575–582.
- St Sauver JL, Grossardt BR, Finney Rutten LJ, et al. Rochester Epidemiology Project Data Exploration Portal. *Prev Chronic Dis*. 2018;15:E42.
- Rocca WA, Yawn BP, St. Sauver JL, Grossardt BR, Melton LJ. History of the Rochester epidemiology project: half a century of medical records linkage in a US population. *Mayo Clin Proc*. 2012;87:1202–1213.
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap)—A metadata driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377–381.
- Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med*. 2003;29:530–538.
- Austin PC, Allignol A, Fine JP. The number of primary events per variable affects estimation of the subdistribution hazard competing risks model. *J Clin Epidemiol*. 2017;83:75–84.
- St Sauver JL, Grossardt BR, Yawn BP, Melton LJ, Rocca WA. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester Epidemiology Project. *Am J Epidemiol*. 2011;173:1059–1068.
- Boam T, Sellars P, Isherwood J, et al. Adherence to vaccination guidelines post splenectomy: a five year follow up study. *J Infect Public Health*. 2017;10:803–808.
- Nived P, Jørgensen CS, Settergren B. Vaccination status and immune response to 13-valent pneumococcal conjugate vaccine in asplenic individuals. *Vaccine*. 2015;33:1688–1694.
- Coignard-Biehler H, Lanternier F, Hot A, et al. Adherence to preventive measures after splenectomy in the hospital setting and in the community. *J Infect Public Health*. 2011;4:187–194.
- Mourtzoukou EG, Pappas G, Peppas G, Falagas ME. Vaccination of asplenic or hyposplenic adults. *Br J Surg*. 2008;95:273–280.
- Smets F, Bourgeois A, Vermeylen C, et al. Randomised revaccination with pneumococcal polysaccharide or conjugate vaccine in asplenic children previously vaccinated with polysaccharide vaccine. *Vaccine*. 2007;25:5278–5282.
- Edgren G, Almqvist R, Hartman M, Utter GH. Splenectomy and the risk of sepsis: a population-based cohort study. *Ann Surg*. 2014;260:1081–1087.
- Ejstrud P, Kristensen B, Hansen JB, Madsen KM, Schonheyder HC, Sorensen H. Risk and patterns of bacteraemia after splenectomy: a population-based study. *Scand J Infect Dis*. 2000;32:521–525.
- Theilacker C, Ludewig K, Serr A, et al. Overwhelming postsplenectomy infection: a prospective multicenter cohort study. *Clin Infect Dis*. 2016;62:871–878.
- Centers for Disease Control. Vaccination of adults with asplenia. <https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/asplenia.html>. Accessed March 31, 2019.

Discussion

Dr Akpofure Peter Ekeh (Dayton, OH): Good afternoon. Thank you, Dr. Hernandez, for a very nice study and presentation. You and your colleagues embarked on this interesting study using the Rochester Epidemiology Project data compiled over a 47-year period. Using data from patients linking them to their hospital records, you determined the rates of post-splenectomy vaccination and the relationship to infection in a single county in Minnesota. This project covered about 97% of the population in Olmsted County, which is quite impressive.

You are to be commended for using a large database to explore important questions that are pertinent to both emergency and elective splenic procedures. You looked at, altogether, 724 patients who had undergone splenectomies for various indications, and you demonstrated a higher risk of infection in patients who did not complete their vaccination. Also, you found patient's infectious risks were also reduced in patients that had complete vaccinations as well as those that had booster vaccines.

I have the following questions for you:

- Do you have any specific information regarding the timing of the vaccines in those patients that received them? Since most of your patients that received splenectomies for malignant indications, many times they do receive vaccinations prior to surgery. Do you have that information from this database and did it make any difference?
- The vast majority of cultures that you obtained in the patients that you reported in your study were from non-capsulated organisms, as noted in one of your tables. Do you have an explanation for this? The vaccinations are specifically targeted at the 3 common capsulated bacterial infections—strep, *pneumoniae*, *N meningitides*, *H influenzae*.
- As acknowledged by the authors, medical care and knowledge has drastically evolved between 1965 and 2011, including the efficacy of antibiotics and the early recognition of sepsis. Did you note a difference over time in the rates of postop infections,



particularly overwhelming post-splenectomy infections? Is that really a rare entity currently, or were most of your infections early on in the study?

4. You demonstrate in one of your figures that in the last decade of your study, which was in the 2000s, there was almost 100% vaccination rate compared to the 1960s when the vaccination rate was less than 25%. So with such high vaccination rates currently, I would ask what is the relevance of the study since everybody seems to be getting vaccinated? Thank you. I enjoyed your paper.

Dr Matthew Hernandez: I'll answer your last question first. We undertook this study because of the antivaccination movement. I think as surgeons, we need to be on top of simple but effective measures to adjust patient outcomes. Anecdotally, on a rotation in a community setting that I'm on right now, I have 2 patients that showed up for trauma and they hadn't been vaccinated in 20 years and hadn't received any information about what they should be doing after their splenectomy.

Additionally, current events in the news show a dramatic push to reduce that type of misinformation. I think we should be loud speakers in the care of these patients, so that's how this study is relevant.

With regard to the timing of vaccination, I do have that data, and I'll add that to the key sentences in the results.

Regarding culture data, a vast majority of the patients in this cohort actually had more than just a splenectomy. They had multivisceral organ resections. So I'm attributing the preponderance of gram-negative infections due to that.

And then, I guess the efficacy question, so, yes, there was an OPSI case in 2008. I can provide that data in the manuscript to further clarify as to the timing of infections. I don't think that the estimated survival curve for the OPSI is not quite that dramatic, but I think for patients to develop any infection, it still is dramatic because you still should be ruling that out as a potential source for infection and morbidity after splenectomy.

Dr Chris McHenry (Cleveland, OH): I have a comment and 2 questions for you. First of all, I think the long-term follow-up that you have for this group of patients is remarkable. My first question is: Can you clarify what the actual incidence of overwhelming post-splenectomy infection was in your cohort?

Secondly, will you please clarify for us when a patient should get a booster?

Dr Matthew Hernandez: The overall rate was 4.4%.

Regarding boosters, in the actual dataset, the booster timing varied. It almost seemed like when people showed up for a primary care visit, around 65, that's when they were getting their boosters. It does not seem that there was a protocol saying you need a booster at 5, 10, 15, or 20 years after splenectomy.

Dr Christopher McHenry: Are there recommendations?

Dr Matthew Hernandez: That I don't know offhand.

Dr Michael Ujiki (Evanston, IL): Very good use of that data, which is important for us, because splenectomy is not the most common operation, so there are not that many databases out there that large that can tell us that.

I'm a little bit worried that the risk of the post-splenectomy sepsis lasts as long as it does, because I do think that's going to be

harder for surgeons to really make an improvement on. We generally are not going to follow people out that long.

I'm wondering if surgeons can maybe effect in a more positive way by finding ways to limit how many times we do splenectomy. In your data, you do show that splenectomy rates are going down. That can be a combination of, for example, better medical treatment of ITP [idiopathic thrombocytopenic purpura]. But in your database, can you get at how many times the spleen was operated on but didn't have a splenectomy? For example, splenic cysts are a common referral to us, and I'm not 100% sure that we know when we should be operating on cysts that look like they are benign and asymptomatic. There's dogma out there about those cysts turning into cancer, and sometimes I see spleens removed that maybe don't need to be. Maybe splenic preserving splenectomies, or in trauma, for example, paying more attention at ways to stop bleeding versus just removing the spleen.

Can you get at that data? Because if you could, that would be interesting to see if we could actually see those rates increase, because I think that's where surgeons can make an effect.

Dr Matthew Hernandez: For the study, we were only allowed to take information from patients who had a splenectomy. But splenic preservation, splenic defenestration, spleen preserving procedures like an embolization, those are all separate ICD-9 [International Classification of Diseases, Ninth Revision] codes and we could feasibly obtain those and redo the study.

Dr Michael Ujiki (Evanston, IL): I don't know if you need to redo it, but that might be a good follow-up study.

Dr Mark Malangoni (Bryn Mawr, PA): I echo the praise that the previous commenters made about your report. It's very well done, and it's nice to have that long perspective.

Thirty-three years ago, we published a similar study looking at only early infection after splenectomy regardless of cause, much like your study, but only tracked patients' infections during their hospitalization. I was fascinated by how similar your data were to ours, at least as far as the organisms that were involved. I wonder if these infections are all early infections that are in the postoperative period after the splenectomy is done or if they occurred later. If you could give us a sense of the percentage that are postop, it would be interesting.

The other comment I would make is that the whole vaccination milieu has changed since our earlier report. There was no meningococcal vaccine. H flu vaccine was just out. Pneumococcal vaccine at that time was a single dose that was effective against a more limited number of strains. Now we have a 2-vaccine system that's used, and is recommended for the elderly, but may fit for your population as well. I wonder if you would comment on both of those points.

Thank you.

Dr Matthew Hernandez: For the infection, I cannot comment without staring at the data regarding the postoperative timing whether it's 1 week, 2 weeks, 3 weeks in the hospital, but that can be easily added to the manuscript to further clarify that.

Then for the vaccines, yes, I think that, obviously, made a huge change in efficacy. There are even studies that show that some patients don't even respond to vaccine despite even administering it. So I think that's some further work to be done, and possibly in a surveillance kind of database that this one might be able to generate. Thank you.