BMJ Open

Vaccine prophylaxis in Apulian splenectomized patients. A retrospective cohort observational study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-069316
Article Type:	Original research
Date Submitted by the Author:	18-Oct-2022
Complete List of Authors:	Bianchi, Francesco; University of Bari, Department of Interdisciplinary Medicine Stefanizzi, Pasquale; Universita degli Studi di Bari Aldo Moro, Department of Interdisciplinary Medicine Di Lorenzo, Antonio; University of Bari, Department of Interdisciplinary Medicine Cuscianna, Eustachio; University of Bari, Department of Interdisciplinary Medicine Tafuri, Silvio; University of Bari, Department of Interdisciplinary Medicine Germinario, Cinzia; Universita degli Studi di Bari Aldo Moro, Department of Interdisciplinary Medicine
Keywords:	Public health < INFECTIOUS DISEASES, PUBLIC HEALTH, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Vaccine prophylaxis in Apulian splenectomized patients. A retrospective cohort observational study.

Authors: Francesco Paolo Bianchi, Pasquale Stefanizzi, Antonio Di Lorenzo, Eustachio Cuscianna, Silvio Tafuri, Cinzia Germinario

Affiliation:

1. Department of Interdisciplinary Medicine, Aldo Moro University of Bari, Bari, Italy

Corresponding author

Silvio Tafuri, MD, PhD

Department of Interdisciplinary Medicine

Aldo Moro University of Bari.

Piazza Giulio Cesare 11, 70124 Bari (Italy)

Phone number: 0039 80 5478473

Fax number: 0039 80 5478472

Mail: silvio.tafuri@uniba.it

Abstract

Objective. Splenectomized/asplenic patients have a tenfold to fiftyfold higher risk than the general population of developing overwhelming post-splenectomy infection. To control this risk, these subjects have to receive a specific immunization schedule, before or in the two weeks after the surgical intervention. The aim of this study was to estimate vaccine coverage (VC) for recommended vaccines among splenectomized patients in Apulia (South Italy).

Design. Retrospective cohort study.

Setting. Apulia, Southern Italy.

Participants. Splenectomized patients.

Methods. The Apulian regional archive of hospital discharge forms (SDOs) was used to define the splenectomized Apulian inhabitants. The study period went from 2015 through 2020. The overall vaccination status of asplenic patients was assessed via data collected from the Regional Immunization Database (GIAVA). The immunization status for anti-*Streptococcus pneumoniae*, anti-*Haemophilus influenzae* type b (Hib), anti-*Neisseria meningitidis* ACYW135, anti-*Neisseria meningitidis* B, and anti-influenza was evaluated.

Results. Since 2015, 1,576 Apulian inhabitants have undergone splenectomy; the VC for anti-*Neisseria meningitidis* B vaccine was 30.9%, for anti-*Neisseria meningitidis* ACYW135 was 27.7%, for anti-*Streptococcus pneumoniae* was 27.0%, for anti-Hib was 30.1%, and 49.2% received at least one dose of flu vaccine before an influenza season after splenectomy.

Conclusions. The results of our study highlight low VC values among Apulian splenectomized patients. The task of public health institutions is to implement new strategies aimed at increasing

vaccination aptitude in this population, implementing educational measures for patients and families, training for GPs and specialists, and ad hoc communication campaigns.

Article summary

Strengths and limitations of this study

- Large sample size (1,576 splenectomized)
- Long study period (6 years)
- Only few published studies have assessed the vaccine coverages in a such large sample of splenectomized patients
- we were unable to evaluate the correlation between vaccine coverages and community care determinants

Keywords: asplenia; immunization prophylaxis; public health; intra-hospital protocol

Word count: 2,360

Abbreviations

CDC: Centers for Disease Control and Prevention

HCW: healthcare worker

OPSI: overwhelming post-splenectomy infection

SDO: hospital discharge forms

INTRODUCTION

Splenectomized/asplenic patients have a tenfold to fiftyfold higher risk than the general population of developing overwhelming post-splenectomy infection (OPSI) caused by encapsulated bacteria such as *Streptococcus pneumoniae* (>50% of cases), *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* [1,2]; the annual cumulative incidence of OPSI is reported ranging from 0.23% to 0.42%, with a lifetime risk of 5% [3]. The risk of OPSI is possibly lifelong [4], but available evidence shows that ˜30% of life-threatening infections occur within the first year and ˜50% within the first 2 years after splenectomy [1].

Asplenic/hyposplenic subjects should be directed towards a routine immunization schedule, in compliance with international vaccination guidelines [5]; indeed, the United States Centers for Diseases Control and Prevention (CDC) [5] strongly recommend the anti-pneumococcal vaccination (a 13-valent conjugate anti-pneumococcal vaccine [PCV13] dose followed at least 8 weeks later by a 23-valent polysaccharide anti-pneumococcal vaccine [PSSV23] dose), the anti-*Haemophilus influenzae* type b vaccine (one dose), the anti-meningococcal ACYW135 (two doses 8 weeks apart and a booster dose once every 5 years), the anti-meningococcal B vaccines (2 or 3 doses, depending on the employed vaccine), the anti-influenza vaccination (1 dose every fall, before the start of the influenza season), the anti-tetanus-diphtheria-acellular pertussis (Tdap) vaccine booster and the anti-Varicella Zoster Virus vaccine [5]. Additional and specific vaccinations should be administered to prevent infections associated with splenic dysfunction based on the patient's clinical conditions and/or vaccination status. Anti-hepatitis A, anti-hepatitis B, anti-measles-mumps-rubella (MMR) and anti-varicella vaccines should therefore be taken into consideration when first visiting an asplenic patient [5].

Guidelines have been updated over the years [6,7], and many studies [8-11] have evidenced the effectiveness and immunogenicity of recommended vaccines in asplenic subjects. Nonetheless,

vaccine coverage (VC) in this population continues to be suboptimal. Indeed, a 2020 meta-analysis [12] showed a 55.1% (95%CI=41.0–69.2%) anti-pneumococcal vaccine coverage (VC), a 48.3% (95%CI=34.3–52.3%) VC for anti-Hib, a 33.7% (95%CI=23.6–43.9%) VC for anti-*Neisseria meningitidis* C/ACYW135, a 13.3% (95%CI=7.0–19.5%) VC for anti-*Neisseria meningitidis* B and a 53.2% (95%CI=22.0–84.4%) VC for anti-influenza vaccination, worldwide. The authors reported that the main determinant of low VCs was a lack of adherence to international guidelines by healthcare workers (HCWs), suggesting the need to better educate health professionals in the management of post-splenectomy patients.

In 2014, Bari Policlinico General Hospital (Apulia, South-East of Italy, ˜4,000,000 inhabitants) approved a specific protocol for actively offering vaccinations to splenectomized patients during their hospitalization [13]. One year after the implementation of the protocol activities, VCs achieved among splenectomized patients had increased tenfold compared to 2013 (from 5.7% to 66.7%). Time from the splenectomy to the beginning of the vaccination protocol had also strongly decreased (from 84.7 to 7.5 days) [13]. During the subsequent years, this protocol was promoted to other major hospitals in Apulia region. In this context, the aim of this study was to estimate VCs for recommended vaccinations among splenectomized patients in Apulia.

METHODS

This is a retrospective observational study. The study population was identified via the Apulian regional archive of hospital discharge forms (SDO), an online database containing all information regarding hospital and inpatient procedures carried out in the whole region [14]. We considered all records referring to splenectomy using the ICD9 code 415.xxx, both in primary and secondary diagnosis, and extended our search to all procedures performed from 2015 throughout 2020. Only

subjects living in Apulia were considered. The following pieces of information were extracted: age at hospitalization, diagnosis at hospitalization, length of hospital stay, and discharge mode.

Lists of deceased Apulian inhabitants (2015-2022) were checked using the Edotto platform (Exprivia, Apulia, Italy) of the Apulian Health Information System. Edotto, set up in 2012, allows the integration of various branches of the Italian healthcare system (Health Department, Regional Health Agency, healthcare companies, general practitioners, pharmacies, hospital physicians, etc.) [15]. The overall vaccination status of asplenic patients was assessed using the Regional Immunization Database (GIAVA) [15]. GIAVA is a computerized vaccination registry containing information on the vaccination history of every Apulian inhabitant; it can also be used to generate an immunization schedule.

These three datasets were extracted and matched using the patients' unique identification numbers (PINs).

The final dataset was created as an Excel spreadsheet that included information on sex, age at splenectomy, characteristics of hospitalization, modality of splenectomy (elective or emergency surgery), death (YES/NO), vaccine prophylaxis (YES/NO) and the type of vaccine. An anonymized data analysis was performed using the STATA MP17 software.

The immunization status for anti-pneumococcal, anti-*Haemophilus influenzae* type b, anti-*Neisseria meningitidis* ACYW135, anti-*Neisseria meningitidis* B, and anti-influenza (1 dose every year, in October/December), considering only subjects surviving for at least 15 days after the surgery, was evaluated. In order to define a subject as fully immunized, we considered completion of CDC guidelines as definition of optimal immunization status [5].

Continuous variables are reported as the mean ± standard deviation and range or median and interquartile range (IQR), and categorical variables as proportions.

To analyse the determinants of anti-pneumococcal, anti-*Haemophilus influenzae* type b, anti-*Neisseria meningitidis* ACYW135, anti-*Neisseria meningitidis* B vaccines uptake (YES/NO) a multivariate logistic regression model was built for each outcome; sex (male vs. female), age at splenectomy (years), length of hospitalization (days) and cause of splenectomy (trauma vs. other) were used as determinants. The adjusted Odds Ratio (aOR) were calculated, as well as 95% Confidence Intervals (95%Cis).

For all tests, a two-sided p-value<0.05 was considered as an indicator of statistical significance.

RESULTS

Since 2015, 1,650 subjects living in Apulia have undergone splenectomy; 1,576 of them (95.5%) were still alive 15 days after the surgery. 923 patients (58.6%) were male and the mean age at splenectomy was 55.9±20.9 years (range: 4-95); 390 out of 1.576 patients (24.7%) reported at least one chronic condition.

Most splenectomies were performed in urgency (n=941; 59.7%), while 635 surgeries (40.3%) had been previously planned; 581 out of 941 urgent splenectomies (61.7%) were required due to traumatic injuries. The median length of hospitalization was 12 days (IQR=7-20), and most patients were discharged at home (n=1.390; 88.2%).

VCs of recommended immunization prophylaxis per year of splenectomy is reported in Table 1.

Table 1. Vaccine coverage (%) per immunization prophylaxis and year of splenectomy.

Year of splenectomy	Anti-meningococcal B (2 doses)	Anti-meningococcal ACYW135 (2 doses)	Anti-pneumococcal (PCV13 + PSSV23)	Anti-Hib	Seasonal flu shot
2015 (n=272)	46 (16.9%)	39 (14.3%)	41 (15.1%)	53 (19.5%)	19/252 (7.5%)
2016 (n=271)	71 (26.2%)	63 (23.3%)	67 (24.7%)	72 (26.6%)	15/487 (3.1%)
2017 (n=276)	80 (29.0%)	66 (23.9%)	59 (21.4%)	112 (40.6%)	28/712 (3.9%)
2018 (n=288)	105 (36.5%)	94 (32.6%)	88 (30.6%)	84 (29.2%)	55/931 (5.9%)
2019 (n=241)	107 (44.4%)	98 (40.7%)	91 (37.8%)	60 (24.9%)	518/1.119 (46.3%)
2020 (n=228)	78 (34.2%)	77 (33.8%)	79 (34.7%)	94 (41.2%)	619/1.291 (47.9%)
Total (n=1.576)	487 (30.9%)	437 (27.7%)	425 (27.0%)	475 (30.1%)	775 (49.2%) *

***at least one seasonal flu shot after splenectomy**

Only 376 patients (23.9%) got their flu shot before all influenza seasons after undergoing splenectomy. None of the subjects splenectomized in 2015 and 2016 received the recommended MenACYW$_{135}$ and PSSV23 booster doses 5 years after completing the basal cycles.

The VC of recommended vaccines per age class is described in Table 2.

Table 2. Vaccine coverage (%) per immunization prophylaxis and age class of patients.

Age class (years)	Anti-meningococcal B (2 doses)	Anti-meningococcal ACYW135 (2 doses)	Anti-pneumococcal (PCV13 + PSSV23)	Anti-Hib	Seasonal flu shot*
0-17 (n=77)	39 (50.7%)	32 (41.6%)	16 (20.8%)	30 (39.0%)	37 (48.1%)
18-64 (n=812)	288 (35.5%)	273 (33.6%)	254 (31.3%)	282 (34.7%)	396 (48.8%)
65+ (n=687)	160 (23.3%)	132 (19.2%)	155 (22.6%)	163 (23.7%)	342 (49.8%)

***at least one seasonal flu shot after splenectomy**

The results of multivariate logistic analyses are reported in Table 3.

Table 3. Analysis of determinants of anti-pneumococcal, anti-*Haemophilus influenzae* type b, anti-*Neisseria meningitidis* ACYW135, anti-*Neisseria meningitidis* B vaccines uptake (YES/NO) through multivariate logistic regression models.

Determinant	Anti-MenB		Anti-MenACYW135		Anti-pneumo		Anti-Hib	
	aOR (95%CI)	p-value	aOR (95%CI)	p-value	aOR (95%CI)	p-value	aOR (95%CI)	p-value
Sex (male vs. female)	1.05 (0.844-1.32)	0.666	1.09 (0.86-1.38)	0.480	1.11 (0.88-1.41)	0.366	0.93 (0.74-1.17)	0.548
Age at splenectomy (yrs)	0.98 (0.97-0.99)	<0.0001	0.99 (0.97-0.99)	<0.0001	1.00 (0.99-1.00)	0.434	0.99 (0.98-0.99)	<0.0001
Length of hospitalization	0.98 (0.97-0.99)	<0.0001	0.98 (0.97-0.99)	<0.0001	0.97 (0.96-0.98)	<0.0001	0.99 (0.98-0.99)	0.002
Cause of splenectomy (trauma vs. other)	0.84 (0.65-1.09)	0.185	0.76 (0.56-0.99)	0.040	0.92 (0.70-1.19)	0.509	1.06 (0.82-1.36)	0.665

The median time from surgery to first vaccine dose was 38 days (IQR=9-100) for anti-MenB, 33 (IQR=8-73) for anti-MenACYW135, 17 (IQR=6-47) for anti-PCV13, and 26 (IQR=19-67) for anti-Hib.

390 out of 1.576 patients (24.7%) died after hospital discharge, with a median time from surgery to death equal to 356 days (IQR=91-825).

CONCLUSIONS

The results of our study highlight low VCs in Apulian splenectomized patients. All VCs are lower than those reported in a 2020 global-level meta-analysis [12], except for the anti-menB vaccine, for which VCs are over twice as high as those reported in literature (13% vs. 31%) [12]. Despite these unsatisfying values, an improvement was observed over the years, with a clearly increasing trend starting from 2015 for all vaccines. The slight decrease in 2020 was likely related to the scarcity of both economic and human resources during the first stage of the COVID-19 pandemic [16].

Stratifying VCs by age group, underage subjects had higher coverages than over-65 patients. Only the anti-influenza vaccine had a similar uptake in all three age classes; this is also confirmed by our multivariate models, that evidenced an inverse correlation between age and prophylaxis uptake (except for anti-pneumococcal vaccination). The values found in minors can be explained by habit: most recommended vaccines are already part of the Italian infant vaccination routine, and physicians are therefore more familiar with these products when children are concerned. On the other hand, VCs in the elderly are worrisome; considering the anti-pneumococcal vaccine, which in Italy is recommended in over-65 subjects regardless of health conditions, such low values are even more of an issue, as they suggest low levels of compliance of both patients and HCWs.

Functional and anatomical asplenia increase susceptibility to infectious diseases, especially in the elderly [17,18]. Low VCs are probably related to a misperception of risk by general practitioners and/or specialized branch physicians. These professionals may in fact identify possible adverse events following immunization as critical risks for vulnerable patients, for whom infections are significantly worse in terms of morbidity and mortality [18].

Time from surgery to the start of vaccination is also longer than desirable: the first days after surgery are in fact characterized by an especially high risk of infections. Although a lack of clinical evidence for efficacy of vaccination in splenectomized individuals is reported in literature and no ideal timings have been defined [19], clinical experience suggests that vaccination protocols should be initiated as soon as possible. Such practice is justified by the latency time required for vaccines to elicit an effective immune response, which for most products is about 20-25 days. Clinical conditions of the patient are to be taken into consideration, as existing evidence recommends administering vaccines only after stabilization of the clinical frame. Moreover, our multivariate analyses showed that a shorter hospital stay is related to higher VCs; this observation is likely related to a tendency of physicians not to vaccinate patients with multiple clinical issues. Subjects necessitating shorter hospital stays are generally easier to treat and are therefore perceived as safer targets for vaccination.

The strengths of our study are the long study period (6 years) and the large population we addressed; to our knowledge, only a few studies in scientific literature investigated this phenomenon on such large samples and for so many years. On the other hand, we were unable to evaluate the correlation between VCs and community care determinants.

A 2021 review identified the lack of skilled HCWs in the field of vaccinology and the unsatisfactory information available for patients, including educational materials, on the importance of vaccination for those with asplenia as two of the major determinants of low

vaccination uptake [12]. The training of healthcare personnel might consist of specific courses, workshops, and events specifically designed for HCWs involved in the management of asplenic patient (surgeons, vaccinologists, GPs). These efforts would benefit not HCWs, but also patients and their caregivers, who would be better informed regarding infections in asplenic individuals.

A multifactorial approach should be implemented to achieve high immunization coverage in this population at risk. The introduction of intra-hospital vaccination protocols for chronic patients has been shown to strongly increase the VC (up to 10-fold) of these individuals [13] and to guarantee a good adherence to prophylaxis recommendations in the years following the splenectomy [20]. When it is not possible to vaccinate in a hospital setting, cooperation between the vaccinologist, physicians from other specialties, and GPs seems to be a determining factor for achieving higher immunization rates in these patients. Currently, the lack of recommendation by GPs and the absence of a clear communication circuit between GPs and branch specialists are considered the main obstacles for these patients' access to immunization. A 2020 French study [21] reported low VCs in a sample of 103 patients splenectomized from 2013 to 2016, concluding that the role of GPs is central in long-term monitoring and management of infections in this population of patients, in collaboration with all healthcare professionals.

At the same time, educating patients about their health condition and the associated risks is crucial [22]. The proposals for improving VCs differed among various experiences in scientific literature, ranging from the use of bracelets to medical records to spleen registries; nevertheless, none of these strategies were reported as sufficiently structured or contextualized to improve the overall management of asplenic patients [12].

In conclusion, VCs in Apulian splenectomized patients are sub-optimal, in line with the values reported in scientific literature for other populations worldwide. The direct consequence of these low VCs is that hundreds of patients are at risk of developing severe vaccine preventable diseases.

Public health institutions need to enforce new strategies aimed at increasing vaccination aptitude in this population, implementing educational measures for patients and families, training for GPs and specialists, and ad hoc communication campaigns. The integration between hospital and community care appears to be fundamental for achieving the goal of protecting this high-risk population.

Statement

Funding

This research was funded by Puglia Regional Observatory of Epidemiology. Grant number: N/A

Conflict of interests

The authors declare that they have no competing interests. The manuscript has not been previously presented in any meeting.

Data sharing statement

Dataset is not available due to privacy restrictions.

Patient and Public Involvement statement

The study was carried out in accordance with the Declaration of Helsinki. It was not possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Ethical approval statement

Ethical review and approval were waived for this study as it constituted public health surveillance and data were routinely collected as per company operative protocol.

Author contribution

FPB designed the study, analyzed the data and drafted the manuscript.

PS and ADL designed the study.

EC contributed to data collection and analysis.

ST and CAG revised the study protocol and the manuscript.

The corresponding author attests that all authors listed meet the criteria for authorship and that no others meeting the criteria have been omitted. All authors have read and approved the manuscript.

REFERENCES

1. Bonanni P, Grazzini M, Niccolai G, et al. Recommended vaccinations for asplenic and hyposplenic adult patients. Hum Vaccin Immunother. 2017;13(2):359–368. .
2. Chong J, Jones P, Spelman D, et al. Overwhelming post-splenectomy sepsis in patients with asplenia and hyposplenia: a retrospective cohort study. Epidemiol Infect. 2017;145(2):397–400.
3. Waghorn DJ. Overwhelming infection in asplenic patients: current best practice preventive measures are not being followed. J Clin Pathol. 2001;54(3):214–218.
4. Sciberras S. Preventing severe infection after splenectomy: what about old splenectomies? BMJ. 2005;331(7516):576.
5. CDC. Asplenia and adult vaccination. [accessed on 2020 Aug 1]. Available on: https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/asplenia.html#:~:text=Asplenia%20and%20Adult%20Vaccination%26text=Tdap%20vaccine%20to%20protect%20against,pneumonia%20and%20other%20pneumococcal%20disease.Last
6. Castagnola E, Fioredda F. Prevention of life-threatening infections due to encapsulated bacteria in children with hyposplenia or asplenia: a brief review of current recommendations for practical purposes. Eur J Haematol. 2003;71(5):319–326.
7. Howdieshell TR, Heffernan D, Dipiro JT. Therapeutic agents committee of the surgical infection society. surgical infection society guidelines for vaccination after traumatic injury. Surg Infect (Larchmt). 2006;7(3):275–303.
8. Martinón-Torres F, Bernatowska E, Shcherbina A, et al. Meningococcal B vaccine immunogenicity in children with defects in complement and splenic function. Pediatrics. 2018;142(3):e20174250. [published correction appears in Pediatrics. 2019 Mar;143(3):]

9. Forstner C, Plefka S, Tobudic S, et al. Effectiveness and immunogenicity of pneumococcal vaccination in splenectomized and functionally asplenic patients. Vaccine. 2012;30(37):5449–5452.
10. Spoulou V, Tzanakaki G, Lekka S, et al. Natural and vaccine-induced immunity to neisseria meningitidis serogroup C in asplenic patients with β-thalassemia. Vaccine. 2011;29(27):4435–4438.
11. Uslu A, Yetiş H, Aykas A, et al. The efficacy and immunogenicity of pneumo-23 and ACT-HIB in patients undergoing splenectomy. . Ulusal travma ve acil cerrahi dergisi = Turkish journal of trauma & emergency surgery. TJTES. 2006;12(4):277–281.
12. Bianchi FP, Stefanizzi P, Spinelli G, Mascipinto S, Tafuri S. Immunization coverage among asplenic patients and strategies to increase vaccination compliance: a systematic review and meta-analysis. Expert Rev Vaccines. 2021 Mar;20(3):297-308.
13. Gallone MS, Martino C, Quarto M, Tafuri S; Bari Policlinico General Hospital. Active offer of vaccinations during hospitalization improves coverage among splenectomized patients: An Italian experience. Am J Infect Control. 2017 Aug 1;45(8):e87-e89.
14. Bianchi FP, Gallone MS, Fortunato F, Boccalini S, Martinelli D, Prato R, Tafuri S. Epidemiology and cost of cervical cancer care and prevention in Apulia (Italy), 2007/2016. Ann Ig. 2018 Nov-Dec;30(6):490-501.
15. Pedote PD, Termite S, Gigliobianco A, Lopalco PL, Bianchi FP. Influenza Vaccination and Health Outcomes in COVID-19 Patients: A Retrospective Cohort Study. Vaccines (Basel). 2021 Apr 8;9(4):358.
16. Deana C, Rovida S, Orso D, et al. Learning from the Italian experience during COVID-19 pandemic waves: be prepared and mind some crucial aspects. *Acta Biomed*. 2021;92(2):e2021097. Published 2021 May 12.

17. Squire JD, Sher M. Asplenia and Hyposplenism: An Underrecognized Immune Deficiency. Immunol Allergy Clin North Am. 2020 Aug;40(3):471-483.

18. Bianchi FP, Tafuri S. Vaccination of Elderly People Affected by Chronic Diseases: A Challenge for Public Health. Vaccines (Basel). 2022 Apr 19;10(5):641.

19. Lenzing E, Rezahosseini O, Burgdorf SK, Nielsen SD, Harboe ZB. Efficacy, immunogenicity, and evidence for best-timing of pneumococcal vaccination in splenectomized adults: a systematic review. Expert Rev Vaccines. 2022 May;21(5):723-733.

20. Bianchi FP, Rizzo LA, De Nitto S, Stefanizzi P, Tafuri S. Influenza vaccination coverage among splenectomized patients: an Italian study on the role of active recall in the vaccination compliance. Hum Vaccin Immunother. 2019;15(11):2644-2649.

21. Quéffélec C, Billet L, Duffau P, Lazaro E, Machelart I, Greib C, Viallard JF, Pellegrin JL, Rivière E. Prevention of infection in asplenic adult patients by general practitioners in France between 2013 and 2016 : Care for the asplenic patient in general practice. BMC Fam Pract. 2020 Aug 12;21(1):163.

22. Gonzalez RA, Robbins JM, Garwe T, Stewart KE, Sarwar Z, Cross AM, Celii AM, Albrecht RM. Effect of Post-splenectomy Booster Vaccine Program on Vaccination Compliance in Trauma Patients. Am Surg. 2021 May;87(5):796-804.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	5-6

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7-11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	7-11
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-11
		(*b*) Report category boundaries when continuous variables were categorized	7-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Vaccine coverage for recommended vaccines among splenectomized patients in Apulia, South Italy: a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-069316.R1
Article Type:	Original research
Date Submitted by the Author:	10-Feb-2023
Complete List of Authors:	Bianchi, Francesco; University of Bari, Department of Interdisciplinary Medicine Stefanizzi, Pasquale; Universita degli Studi di Bari Aldo Moro, Department of Interdisciplinary Medicine Di Lorenzo, Antonio; University of Bari, Department of Interdisciplinary Medicine Cuscianna, Eustachio; University of Bari, Department of Interdisciplinary Medicine Tafuri, Silvio; University of Bari, Department of Interdisciplinary Medicine Germinario, Cinzia; Universita degli Studi di Bari Aldo Moro, Department of Interdisciplinary Medicine
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Infectious diseases, Evidence based practice, Haematology (incl blood transfusion)
Keywords:	Public health < INFECTIOUS DISEASES, PUBLIC HEALTH, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Vaccine coverage for recommended vaccines among splenectomized patients in Apulia, South Italy: a retrospective cohort study

Authors: Francesco Paolo Bianchi, Pasquale Stefanizzi, Antonio Di Lorenzo, Eustachio Cuscianna, Silvio Tafuri, Cinzia Germinario

Affiliation:

1. Department of Interdisciplinary Medicine, Aldo Moro University of Bari, Bari, Italy

Corresponding author

Silvio Tafuri, MD, PhD

Department of Interdisciplinary Medicine

Aldo Moro University of Bari.

Piazza Giulio Cesare 11, 70124 Bari (Italy)

Phone number: 0039 80 5478473

Fax number: 0039 80 5478472

Mail: silvio.tafuri@uniba.it

Abstract

Objective. Splenectomized/asplenic patients have a tenfold to fiftyfold higher risk than the general population of developing overwhelming post-splenectomy infection. To control this risk, these subjects have to receive a specific immunization schedule, before or in the two weeks after the surgical intervention. The study aims to estimate vaccine coverage (VC) for recommended vaccines among splenectomized patients in Apulia (South Italy), and to define the determinants of vaccination uptake in this sub-group population.

Design. Retrospective cohort study.

Setting. Apulia, Southern Italy.

Participants. 1,576 splenectomized patients.

Methods. The Apulian regional archive of hospital discharge forms (SDOs) was used to define the splenectomized Apulian inhabitants. The study period went from 2015 through 2020. The vaccination status for *Streptococcus pneumoniae* (PCV13 + PSSV23), *Haemophilus influenzae* type b (Hib; 1 dose), *Neisseria meningitidis* ACYW135 (2 doses), *Neisseria meningitidis* B (2 doses), and influenza (at least one dose of flu vaccine before an influenza season after splenectomy) was assessed via data collected from the Regional Immunization Database (GIAVA). In order to define a subject as fully immunized, we considered the Center for Diseases Control and Prevention guidelines to define the optimal immunization status.

Results. Since 2015, 1,576 Apulian inhabitants have undergone splenectomy; the VC for anti-*Neisseria meningitidis* B vaccine was 30.9%, for anti-*Neisseria meningitidis* ACYW135 was 27.7%, for anti-*Streptococcus pneumoniae* was 27.0%, for anti-Hib was 30.1%, and 49.2% received at least one dose of flu vaccine before an influenza season after splenectomy. None of the subjects

splenectomized in 2015 and 2016 received the recommended MenACYW$_{135}$ and PSSV23 booster doses 5 years after completing the basal cycles.

Conclusions. The results of our study highlight low VC values among Apulian splenectomized patients. The task of public health institutions is to implement new strategies aimed at increasing vaccination aptitude in this population, implementing educational measures for patients and families, training for GPs and specialists, and ad hoc communication campaigns.

Article summary

Strengths and limitations of this study

- Large sample size (1,576 splenectomized)
- Long study period (6 years)
- The Edotto platform is built for administrative and non-epidemiological purposes
- We were unable to evaluate the correlation between vaccine coverages and community care determinants
- Splenectomized subjects may have changed Region or country after the surgery

Keywords: asplenia; immunization prophylaxis; public health; intra-hospital protocol

Word count: 2,360

Abbreviations

CDC: Centers for Disease Control and Prevention

HCW: healthcare worker

OPSI: overwhelming post-splenectomy infection

SDO: hospital discharge forms

INTRODUCTION

Splenectomized/asplenic patients have a tenfold to fiftyfold higher risk than the general population of developing overwhelming post-splenectomy infection (OPSI) caused by encapsulated bacteria such as *Streptococcus pneumoniae* (>50% of cases), *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* [1,2]; the annual cumulative incidence of OPSI is reported ranging from 0.23% to 0.42%, with a lifetime risk of 5% [3]. The risk of OPSI is possibly lifelong [4], but available evidence shows that ˜30% of life-threatening infections occur within the first year and ˜50% within the first 2 years after splenectomy [1].

Asplenic/hyposplenic subjects should be directed towards a routine immunization schedule, in compliance with international vaccination guidelines [5]; indeed, the United States Centers for Diseases Control and Prevention (CDC) [5] strongly recommend the anti-pneumococcal vaccination (a 13-valent conjugate anti-pneumococcal vaccine [PCV13] dose followed at least 8 weeks later by a 23-valent polysaccharide anti-pneumococcal vaccine [PSSV23] dose), the anti-*Haemophilus influenzae* type b vaccine (one dose), the anti-meningococcal ACYW135 (two doses 8 weeks apart and a booster dose once every 5 years), the anti-meningococcal B vaccines (2 or 3 doses, depending on the employed vaccine), the anti-influenza vaccination (1 dose every fall, before the start of the influenza season), the anti-tetanus-diphtheria-acellular pertussis (Tdap) vaccine booster and the anti-Varicella Zoster Virus vaccine [5]. Additional and specific vaccinations should be administered to prevent infections associated with splenic dysfunction based on the patient's clinical conditions and/or vaccination status. Anti-hepatitis A, anti-hepatitis B, anti-measles-mumps-rubella (MMR) and anti-varicella vaccines should therefore be taken into consideration when first visiting an asplenic patient [5].

Guidelines have been updated over the years [6,7], and many studies [8-11] have evidenced the effectiveness and immunogenicity of recommended vaccines in asplenic subjects. Nonetheless,

vaccine coverage (VC) in this population continues to be suboptimal. Indeed, a 2020 meta-analysis [12] showed a 55.1% (95%CI=41.0–69.2%) anti-pneumococcal vaccine coverage (VC), a 48.3% (95%CI=34.3–52.3%) VC for anti-Hib, a 33.7% (95%CI=23.6–43.9%) VC for anti-*Neisseria meningitidis* C/ACYW135, a 13.3% (95%CI=7.0–19.5%) VC for anti-*Neisseria meningitidis* B and a 53.2% (95%CI=22.0–84.4%) VC for anti-influenza vaccination, worldwide. The authors reported that the focal factor of low VCs was a lack of observance to international guidelines by healthcare workers (HCWs), suggesting the need to improve educatation of health personnel in the management of post-splenectomy patients.

In 2014, Bari Policlinico General Hospital (Apulia, Southern Italy, ˜4,000,000 inhabitants) approved a specific protocol for actively offering vaccinations to splenectomized patients during their hospitalization [13]. One year after the implementation of the protocol activities, VCs achieved among these patients had increased tenfold compared to 2013 (from 5.7% to 66.7%). Time from the splenectomy procedure to the beginning of the vaccination protocol also strongly decreased (from 84.7 days in 2013 to 7.5 days after the implementation of the protocol) [13]. During the subsequent years, this protocol was promoted to other major hospitals in Apulia region. In this context, this study aimed to estimate VCs for recommended vaccinations among splenectomized patients in Apulia.

METHODS

This is a retrospective observational study. The study population was identified via the Apulian regional archive of hospital discharge forms (SDO), an online database containing all information regarding hospital and inpatient procedures carried out in the whole region [14]. We considered all records referring to splenectomy using the ICD9 code 41.5, and extended our search to all procedures performed from 2015 throughout 2020. Only subjects living in Apulia were considered.

The following pieces of information were extracted: age at hospitalization, diagnosis at hospitalization, length of hospital stay, and discharge mode.

Lists of deceased Apulian inhabitants (2015-2022) were checked using the Edotto platform (Exprivia, Apulia, Italy) of the Apulian Health Information System [15]. The vaccination status of asplenic patients was assessed using the Regional Immunization Database (GIAVA) [15]. GIAVA is a digital vaccination registry containing information on the vaccination history of every Apulian inhabitant.

These three datasets were extracted and matched using the patients' unique identification numbers (PINs).

The final dataset was built as an Excel spreadsheet that integrated info on sex, age at splenectomy, characteristics of hospitalization, modality of splenectomy (elective or emergency surgery), death (YES/NO), vaccine prophylaxis (YES/NO) and the type of vaccine. An anonymized data analysis was performed using the STATA MP17 software.

The vaccination status for anti-pneumococcal, anti-*Haemophilus influenzae* type b, anti-*Neisseria meningitidis* ACYW135, anti-*Neisseria meningitidis* B, and anti-influenza (1 dose every year, in October/December), considering only subjects surviving for at least 15 days after the surgery, was evaluated. In order to define a subject as fully immunized, we considered completion of CDC guidelines as the definition of optimal immunization status [5].

Continuous variables were reported as the mean ± standard deviation and range or median and interquartile range (IQR), and categorical variables as proportions.

To analyse the determinants of anti-pneumococcal, anti-*Haemophilus influenzae* type b, anti-*Neisseria meningitidis* ACYW135, anti-*Neisseria meningitidis* B, and anti-influenza (a flu shot before each flu season that followed the splenectomy) vaccines uptake (YES/NO) a multivariate logistic regression model was built for each outcome; sex (male vs. female), age at splenectomy

(years), length of hospitalization (days) and cause of splenectomy (trauma vs. other) were used as determinants. The adjusted Odds Ratios (aOR) were calculated, as well as 95% Confidence Intervals (95%Cis).

For all tests, a two-sided p-value<0.05 was considered an indicator of statistical significance.

Patient and Public Involvement

None

RESULTS

Since 2015, 1,650 subjects living in Apulia have undergone splenectomy; 1,576 of them (95.5%) were still alive 15 days after the surgery (Figure 1).

Figure 1. Flowchart of computation of final sample size.

923 patients (58.6%) were male and the mean age at splenectomy was 55.9±20.9 years (range: 4-95); 390 out of 1.576 patients (24.7%) reported at least one chronic condition.

Most splenectomies were performed in urgency (n=941; 59.7%), while 635 surgeries (40.3%) had been previously planned; 581 out of 941 urgent splenectomies (61.7%) were required due to traumatic injuries. The median length of hospitalization was 12 days (IQR=7-20), and most patients were discharged (n=1.390; 88.2%).

VCs of recommended immunization prophylaxis per year of splenectomy are reported in Table 1; only 343 (21.1%) subjects received the seasonal flu shot before each influenza season that followed splenectomy.

Table 1. Vaccine coverage (%) per immunization prophylaxis and year of splenectomy.

Year of splenectomy	Anti-meningococcal B (2 doses)	Anti-meningococcal ACYW135 (2 doses)	Anti-pneumococcal (PCV13 + PSSV23)	Anti-Hib	Seasonal flu shot*
2015 (n=272)	46 (16.9%)	39 (14.3%)	41 (15.1%)	53 (19.5%)	104 (38.2%)
2016 (n=271)	71 (26.2%)	63 (23.3%)	67 (24.7%)	72 (26.6%)	114 (42.1%)
2017 (n=276)	80 (29.0%)	66 (23.9%)	59 (21.4%)	112 (40.6%)	122 (44.2%)
2018 (n=288)	105 (36.5%)	94 (32.6%)	88 (30.6%)	84 (29.2%)	152 (52.8%)
2019 (n=241)	107 (44.4%)	98 (40.7%)	91 (37.8%)	60 (24.9%)	150 (62.2%)
2020 (n=228)	78 (34.2%)	77 (33.8%)	79 (34.7%)	94 (41.2%)	133 (58.3%)
Total (n=1.576)	487 (30.9%)	437 (27.7%)	425 (27.0%)	475 (30.1%)	775 (49.2%)

***at least one seasonal flu shot after splenectomy**

Only 376 patients (23.9%) got their flu shot before all influenza seasons after undergoing splenectomy. None of the subjects splenectomized in 2015 and 2016 received the recommended MenACYW$_{135}$ and PSSV23 booster doses 5 years after completing the basal cycles.

The VC of recommended vaccines per age class is described in Table 2.

Table 2. Vaccine coverage (%) per immunization prophylaxis and age class of patients.

Age class (years)	Anti-meningococcal B (2 doses)	Anti-meningococcal ACYW135 (2 doses)	Anti-pneumococcal (PCV13 + PSSV23)	Anti-Hib	Seasonal flu shot*
0-17 (n=77)	39 (50.7%)	32 (41.6%)	16 (20.8%)	30 (39.0%)	37 (48.1%)
18-64 (n=812)	288 (35.5%)	273 (33.6%)	254 (31.3%)	282 (34.7%)	396 (48.8%)
65+ (n=687)	160 (23.3%)	132 (19.2%)	155 (22.6%)	163 (23.7%)	342 (49.8%)

***at least one seasonal flu shot after splenectomy**

The results of multivariate logistic analyses are reported in Table 3.

Table 3. Analysis of determinants of anti-pneumococcal, anti-*Haemophilus influenzae* type b, anti-*Neisseria meningitidis* ACYW135, anti-*Neisseria meningitidis* B vaccines uptake (YES/NO) through multivariate logistic regression models.

Determinant	Anti-MenB		Anti-MenACYW135		Anti-pneumo		Anti-Hib		Flu vaccine*	
	aOR (95%CI)	p-value	aOR (95%CI)	p-value	aOR (95%CI)	p-value	aOR (95%CI)	p-value	aOR (95%CI)	p-value
Sex (male vs. female)	1.05 (0.84-1.32)	0.666	1.09 (0.86-1.38)	0.480	1.11 (0.88-1.41)	0.366	0.93 (0.74-1.17)	0.548	0.91 (0.70-1.17)	0.454
Age at splenectomy (yrs)	0.98 (0.97-0.99)	<0.0001	0.99 (0.97-0.99)	<0.0001	1.00 (0.99-1.00)	0.434	0.99 (0.98-0.99)	<0.0001	1.01 (0.99-1,01)	0.084
Length of hospitalization	0.98 (0.97-0.99)	<0.0001	0.98 (0.97-0.99)	<0.0001	0.97 (0.96-0.98)	<0.0001	0.99 (0.98-0.99)	0.002	0.98 (0.97-0.99)	0.001
Cause of splenectomy (trauma vs. other)	0.84 (0.65-1.09)	0.185	0.76 (0.56-0.99)	0.040	0.92 (0.70-1.19)	0.509	1.06 (0.82-1.36)	0.665	1.05 (0.80-1.40)	0.716

***a flu shot before each flu season that followed the splenectomy**

The median time from surgery to the first vaccine dose was 38 days (IQR=9-100) for anti-MenB, 33 (IQR=8-73) for anti-MenACYW135, 17 (IQR=6-47) for anti-PCV13, and 26 (IQR=19-67) for anti-Hib.

445 out of 1.576 patients (28.2%) died after hospital discharge, with a median time from surgery to death equal to 356 days (IQR=91-825).

CONCLUSIONS

The results of our study highlight low VCs in Apulian splenectomized patients. All VCs are lower than those reported in a 2020 global-level meta-analysis [12], except for the anti-menB vaccine, for which VCs are over twice as high as those reported in the literature (13% vs. 31%) [12]. Despite these unsatisfying values, an improvement was observed over the years, with an increasing trend starting from 2015 for all vaccines. The slight decrease in 2020 was likely related to the scarcity of both economic and human resources during the first stage of the COVID-19 pandemic [16].

Stratifying VCs by age group, younger subjects had higher coverages than over-65 patients. Only the anti-influenza vaccine had a similar uptake in all three age classes; this is also confirmed by our multivariate models, which evidenced an inverse correlation between age and prophylaxis uptake (except for anti-pneumococcal vaccination). The values found in minors can be explained by habit: most recommended vaccines are already part of the Italian infant vaccination routine, and physicians are therefore more familiar with these products when children are concerned. On the other hand, VCs in the elderly are worrisome; considering the anti-pneumococcal vaccine, which in Italy is recommended in over 65 subjects regardless of health conditions, such low values are even more of an issue, as they suggest low levels of compliance of both patients and HCWs.

Functional and anatomical asplenia increase susceptibility to infectious diseases, especially in the elderly [17,18]. Low VCs are probably related to a misperception of risk by general practitioners and/or specialized branch physicians. These professionals may identify possible adverse events following immunization as critical risks for vulnerable patients, for whom infections are significantly worse in terms of morbidity and mortality [18].

Time from surgery to the start of vaccination is also longer than desirable: the first days after surgery are characterized by an especially high risk of infections. Although a lack of clinical evidence for the effectiveness of vaccination in splenectomized individuals is reported in the literature and no ideal timings have been defined [19], clinical experience suggests that vaccination protocols should be initiated as soon as possible. Such practice is justified by the latency time required for vaccines to elicit an effective immune response, which for most products is about 20-25 days. Clinical conditions of the patient are to be taken into consideration, as existing evidence recommends administering vaccines only after stabilization of the clinical frame. Moreover, our multivariate analyses showed that a shorter hospital stay is related to higher VCs; this observation is likely related to a tendency of physicians not to vaccinate patients with multiple comorbidities, and therefore perceived as frailer. Subjects requiring shorter hospital stays are generally easier to treat and are therefore perceived as safer targets for vaccination. Surprisingly, splenectomies caused by malignancies seem to be associated with a better uptake of MenACYW135 vaccine; this could be a statistical artifact, and more investigation is needed to clarify this point.

The strengths of our study are the long study period (6 years) and the large population we addressed; to our knowledge, only a few studies in scientific literature investigated this phenomenon on such large samples and for so many years. On the other hand, we were unable to evaluate the correlation between VCs and community care determinants. Moreover, the Edotto platform is built for administrative and non-epidemiological purposes, so there is a theoretical risk

of bias; this risk is low, considering that all the healthcare information data in Apulia are digitized, and therefore our methodology is not affected by this issue. Finally, there is a theoretical risk that splenectomized subjects may have changed Region or country after the surgery, and therefore we could not record the vaccinations eventually administered.

A 2021 review identified the lack of skilled HCWs in the field of vaccinology and the unsatisfactory information available for patients, including educational materials, on the importance of vaccination for those with asplenia as two of the major determinants of low vaccination uptake [12]. The training of healthcare personnel might consist of specific courses, workshops, and events specifically designed for HCWs involved in the management of the asplenic patient (surgeons, vaccinologists, GPs). These efforts would benefit not HCWs, but also patients and their caregivers, who would be better informed regarding infections in asplenic individuals.

A multifactorial approach should be implemented to achieve high immunization coverage in this population at risk. The introduction of intra-hospital vaccination protocols for chronic patients has been shown to strongly increase the VC (up to 10-fold) of these individuals [13] and to guarantee good adherence to prophylaxis recommendations in the years following the splenectomy [20]. When it is not possible to vaccinate in a hospital setting, cooperation between the vaccinologist, physicians from other specialties, and GPs seems to be a determining factor for achieving higher immunization rates in these patients. Currently, the lack of recommendations by GPs and the absence of a clear communication circuit between GPs and branch specialists are considered the main obstacles to these patients' access to immunization. A 2020 French study [21] reported low VCs in a sample of 103 patients splenectomized from 2013 to 2016, concluding that the role of GPs is central in the long-term monitoring and management of infections in this population of patients, in collaboration with all healthcare professionals.

At the same time, educating patients about their health conditions and the associated risks is crucial [22]. The proposals for improving VCs differed among various experiences in the scientific literature, ranging from the use of bracelets to medical records to spleen registries; nevertheless, none of these strategies were reported as sufficiently structured or contextualized to improve the overall management of asplenic patients [12].

In conclusion, VCs in Apulian splenectomized patients are sub-optimal, in line with the values reported in scientific literature for other populations worldwide. The direct consequence of these low VCs is that hundreds of patients are at risk of developing severe vaccine-preventable diseases. Public health institutions need to enforce new approaches aimed at increasing vaccination aptitude in this population, implementing educational measures for patients and families, education for GPs and specialists, and ad hoc communication campaigns. The integration between hospital and community care appears to be fundamental for achieving the goal of protecting this high-risk population. In the future new techniques and scientific innovations, such as the experimental reinfusion of splenic lymphocytes in splenectomized patients [23], could help to reduce the morbidity and mortality in asplenic subjects; till then the vaccination prophylaxis of splenectomized subjects is the main preventive tool to avoid infections' complications in these patients.

Statement

Funding

This research was funded by the Apulia Regional Observatory of Epidemiology. Grant number: N/A

Conflict of interests

The authors declare that they have no competing interests.

Data sharing statement

The dataset is not available due to privacy restrictions.

Ethical approval statement

The present study did not require ethical approval for its observational design according to Italian law (Gazzetta Ufficiale no. 76 dated March 3, 2008). The study was carried out in accordance with the Declaration of Helsinki.

Author contribution

FPB designed the study, analyzed the data, and drafted the manuscript.

PS and ADL designed the study.

EC contributed to data collection and analysis.

ST and CAG revised the study protocol and the manuscript.

The corresponding author attests that all authors listed meet the criteria for authorship and that no others meeting the criteria have been omitted. All authors have read and approved the manuscript.

REFERENCES

1. Bonanni P, Grazzini M, Niccolai G, et al. Recommended vaccinations for asplenic and hyposplenic adult patients. Hum Vaccin Immunother. 2017;13(2):359–368. .
2. Chong J, Jones P, Spelman D, et al. Overwhelming post-splenectomy sepsis in patients with asplenia and hyposplenia: a retrospective cohort study. Epidemiol Infect. 2017;145(2):397–400.
3. Waghorn DJ. Overwhelming infection in asplenic patients: current best practice preventive measures are not being followed. J Clin Pathol. 2001;54(3):214–218.
4. Sciberras S. Preventing severe infection after splenectomy: what about old splenectomies? BMJ. 2005;331(7516):576.
5. CDC. Asplenia and adult vaccination. [accessed on 2020 Aug 1]. Available on: https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/asplenia.html#:~:text=Asplenia%20and%20Adult%20Vaccination%26text=Tdap%20vaccine%20to%20protect%20against,pneumonia%20and%20other%20pneumococcal%20disease.Last
6. Castagnola E, Fioredda F. Prevention of life-threatening infections due to encapsulated bacteria in children with hyposplenia or asplenia: a brief review of current recommendations for practical purposes. Eur J Haematol. 2003;71(5):319–326.
7. Howdieshell TR, Heffernan D, Dipiro JT. Therapeutic agents committee of the surgical infection society. surgical infection society guidelines for vaccination after traumatic injury. Surg Infect (Larchmt). 2006;7(3):275–303.
8. Martinón-Torres F, Bernatowska E, Shcherbina A, et al. Meningococcal B vaccine immunogenicity in children with defects in complement and splenic function. Pediatrics. 2018;142(3):e20174250. [published correction appears in Pediatrics. 2019 Mar;143(3):]

9. Forstner C, Plefka S, Tobudic S, et al. Effectiveness and immunogenicity of pneumococcal vaccination in splenectomized and functionally asplenic patients. Vaccine. 2012;30(37):5449–5452.
10. Spoulou V, Tzanakaki G, Lekka S, et al. Natural and vaccine-induced immunity to neisseria meningitidis serogroup C in asplenic patients with β-thalassemia. Vaccine. 2011;29(27):4435–4438.
11. Uslu A, Yetiş H, Aykas A, et al. The efficacy and immunogenicity of pneumo-23 and ACT-HIB in patients undergoing splenectomy. . Ulusal travma ve acil cerrahi dergisi = Turkish journal of trauma & emergency surgery. TJTES. 2006;12(4):277–281.
12. Bianchi FP, Stefanizzi P, Spinelli G, Mascipinto S, Tafuri S. Immunization coverage among asplenic patients and strategies to increase vaccination compliance: a systematic review and meta-analysis. Expert Rev Vaccines. 2021 Mar;20(3):297-308.
13. Gallone MS, Martino C, Quarto M, Tafuri S; Bari Policlinico General Hospital. Active offer of vaccinations during hospitalization improves coverage among splenectomized patients: An Italian experience. Am J Infect Control. 2017 Aug 1;45(8):e87-e89.
14. Bianchi FP, Gallone MS, Fortunato F, Boccalini S, Martinelli D, Prato R, Tafuri S. Epidemiology and cost of cervical cancer care and prevention in Apulia (Italy), 2007/2016. Ann Ig. 2018 Nov-Dec;30(6):490-501.
15. Pedote PD, Termite S, Gigliobianco A, Lopalco PL, Bianchi FP. Influenza Vaccination and Health Outcomes in COVID-19 Patients: A Retrospective Cohort Study. Vaccines (Basel). 2021 Apr 8;9(4):358.
16. Deana C, Rovida S, Orso D, et al. Learning from the Italian experience during COVID-19 pandemic waves: be prepared and mind some crucial aspects. *Acta Biomed*. 2021;92(2):e2021097. Published 2021 May 12.

17. Squire JD, Sher M. Asplenia and Hyposplenism: An Underrecognized Immune Deficiency. Immunol Allergy Clin North Am. 2020 Aug;40(3):471-483.

18. Bianchi FP, Tafuri S. Vaccination of Elderly People Affected by Chronic Diseases: A Challenge for Public Health. Vaccines (Basel). 2022 Apr 19;10(5):641.

19. Lenzing E, Rezahosseini O, Burgdorf SK, Nielsen SD, Harboe ZB. Efficacy, immunogenicity, and evidence for best-timing of pneumococcal vaccination in splenectomized adults: a systematic review. Expert Rev Vaccines. 2022 May;21(5):723-733.

20. Bianchi FP, Rizzo LA, De Nitto S, Stefanizzi P, Tafuri S. Influenza vaccination coverage among splenectomized patients: an Italian study on the role of active recall in the vaccination compliance. Hum Vaccin Immunother. 2019;15(11):2644-2649.

21. Quéffélec C, Billet L, Duffau P, Lazaro E, Machelart I, Greib C, Viallard JF, Pellegrin JL, Rivière E. Prevention of infection in asplenic adult patients by general practitioners in France between 2013 and 2016 : Care for the asplenic patient in general practice. BMC Fam Pract. 2020 Aug 12;21(1):163.

22. Gonzalez RA, Robbins JM, Garwe T, Stewart KE, Sarwar Z, Cross AM, Celii AM, Albrecht RM. Effect of Post-splenectomy Booster Vaccine Program on Vaccination Compliance in Trauma Patients. Am Surg. 2021 May;87(5):796-804.

23. Li SC, Kabeer MH. Autologous Splenocyte Reinfusion Improves Antibody-Mediated Immune Response to the 23-Valent Pneumococcal Polysaccharide-Based Vaccine in Splenectomized Mice. Biomolecules. 2020 May 1;10(5):704.

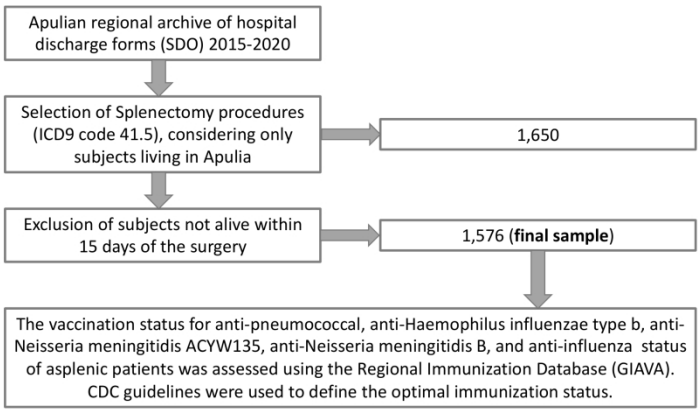

Figure 1. Flowchart of computation of final sample size.

857x482mm (79 x 79 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	5-6

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7-11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-11
		(*b*) Report category boundaries when continuous variables were categorized	7-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Vaccine coverage for recommended vaccines among splenectomized patients in Apulia, South Italy: a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-069316.R2
Article Type:	Original research
Date Submitted by the Author:	17-Mar-2023
Complete List of Authors:	Bianchi, Francesco; University of Bari, Department of Interdisciplinary Medicine Stefanizzi, Pasquale; Universita degli Studi di Bari Aldo Moro, Department of Interdisciplinary Medicine Di Lorenzo, Antonio; University of Bari, Department of Interdisciplinary Medicine Cuscianna, Eustachio; University of Bari, Department of Interdisciplinary Medicine Tafuri, Silvio; University of Bari, Department of Interdisciplinary Medicine Germinario, Cinzia; Universita degli Studi di Bari Aldo Moro, Department of Interdisciplinary Medicine
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Infectious diseases, Evidence based practice, Haematology (incl blood transfusion)
Keywords:	Public health < INFECTIOUS DISEASES, PUBLIC HEALTH, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Vaccine coverage for recommended vaccines among splenectomized patients in Apulia, South Italy: a retrospective cohort study

Francesco Paolo Bianchi,[1] Pasquale Stefanizzi,[1] Antonio Di Lorenzo,[1] Eustachio Cuscianna,[1] Silvio Tafuri,[1] Cinzia Annatea Germinario[1]

Affiliations:

1. Department of Interdisciplinary Medicine, Aldo Moro University of Bari, Bari, Italy

Correspondence to:

Silvio Tafuri, MD, PhD

Department of Interdisciplinary Medicine, Aldo Moro University of Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy

silvio.tafuri@uniba.it

Abstract

Objective: Splenectomized/asplenic patients have a tenfold to fiftyfold higher risk than the general population of developing overwhelming post-splenectomy infection. To control this risk, these patients have to receive a specific immunization schedule, before or in the two weeks after the surgical intervention. The study aims to estimate vaccine coverage (VC) for recommended vaccines among splenectomized patients in Apulia (South Italy), and to define the determinants of vaccination uptake in this population.

Design: Retrospective cohort study.

Setting: Apulia, Southern Italy.

Participants: 1,576 splenectomized patients.

Methods: The Apulian regional archive of hospital discharge forms (SDOs) was used to define the splenectomized Apulian inhabitants. The study period went from 2015 through 2020. The vaccination status for *Streptococcus pneumoniae* (PCV13 + PSSV23), *Haemophilus influenzae* type b (Hib; 1 dose), *Neisseria meningitidis* ACYW135 (2 doses), *Neisseria meningitidis* B (2 doses), and influenza (at least one dose of flu vaccine before an influenza season after splenectomy) was assessed via data collected from the Regional Immunization Database (GIAVA). In order to define a subject as fully immunized, we considered the Center for Diseases Control and Prevention guidelines to define the optimal immunization status.

Results: Since 2015, 1,576 Apulian inhabitants have undergone splenectomy; the VC for anti-*Neisseria meningitidis* B vaccine was 30.9%, for anti-*Neisseria meningitidis* ACYW135 was 27.7%, for anti-*Streptococcus pneumoniae* was 27.0%, for anti-Hib was 30.1%, and 49.2% received at least one dose of flu vaccine before an influenza season after splenectomy. None of the patients

splenectomized in 2015 and 2016 had received the recommended MenACYW$_{135}$ and PSSV23 booster doses 5 years after completing the basal cycles.

Conclusions: The results of our study highlight low VC values among Apulian splenectomized patients. The task of public health institutions is to implement new strategies aimed at increasing VC in this population, implementing educational measures for patients and families, training for GPs and specialists, and ad hoc communication campaigns.

Strengths and limitations of this study

- Large sample size (1,576 splenectomized patients).
- Long study period (6 years).
- The Edotto platform is built for administrative and non-epidemiological purposes.
- We were unable to evaluate the correlation between vaccine coverages and community care determinants.
- Some splenectomized patients may have changed region or country after the surgery.

Keywords: asplenia; immunization prophylaxis; public health; intra-hospital protocol

Word count: 2,360

Abbreviations

CDC: Centers for Disease Control and Prevention

HCW: healthcare worker

OPSI: overwhelming post-splenectomy infection

SDO: hospital discharge forms

INTRODUCTION

Splenectomized/asplenic patients have a tenfold to fiftyfold higher risk than the general population of developing overwhelming post-splenectomy infection (OPSI) caused by encapsulated bacteria such as *Streptococcus pneumoniae* (>50% of cases), *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* [1,2]; the annual cumulative incidence of OPSI is reported ranging from 0.23% to 0.42%, with a lifetime risk of 5% [3]. The risk of OPSI is possibly lifelong [4], but available evidence shows that ˜30% of life-threatening infections occur within the first year and ˜50% within the first 2 years after splenectomy [1].

Asplenic/hyposplenic subjects should be directed towards a routine immunization schedule, in compliance with international vaccination guidelines [5]; indeed, the United States Centers for Diseases Control and Prevention (CDC) [5] strongly recommend the anti-pneumococcal vaccination (a 13-valent conjugate anti-pneumococcal vaccine [PCV13] dose followed at least 8 weeks later by a 23-valent polysaccharide anti-pneumococcal vaccine [PSSV23] dose), the anti-*Haemophilus influenzae* type b vaccine (one dose), the anti-meningococcal ACYW135 (two doses 8 weeks apart and a booster dose once every 5 years), the anti-meningococcal B vaccines (2 or 3 doses, depending on the employed vaccine), the anti-influenza vaccination (1 dose every fall, before the start of the influenza season), the anti-tetanus-diphtheria-acellular pertussis (Tdap) vaccine booster and the anti-Varicella Zoster Virus vaccine [5]. Additional and specific vaccinations should be administered to prevent infections associated with splenic dysfunction based on the patient's clinical conditions and/or vaccination status. Anti-hepatitis A, anti-hepatitis B, anti-measles-mumps-rubella (MMR) and anti-varicella vaccines should therefore be taken into consideration when first visiting an asplenic patient [5].

Guidelines have been updated over the years [6,7], and many studies [8-11] have evidenced the effectiveness and immunogenicity of recommended vaccines in asplenic subjects. Nonetheless,

vaccine coverage (VC) in this population continues to be suboptimal. Indeed, a 2020 meta-analysis [12] showed a 55.1% (95%CI=41.0–69.2%) anti-pneumococcal vaccine coverage (VC), a 48.3% (95%CI=34.3–52.3%) VC for anti-Hib, a 33.7% (95%CI=23.6–43.9%) VC for anti-*Neisseria meningitidis* C/ACYW135, a 13.3% (95%CI=7.0–19.5%) VC for anti-*Neisseria meningitidis* B and a 53.2% (95%CI=22.0–84.4%) VC for anti-influenza vaccination, worldwide. The authors reported that the focal factor of low VCs was a lack of observance to international guidelines by healthcare workers (HCWs), suggesting the need to improve education of health personnel in the management of post-splenectomy patients.

In 2014, Bari Policlinico General Hospital (Apulia, Southern Italy, ˜4,000,000 inhabitants) approved a specific protocol for actively offering vaccinations to splenectomized patients during their hospitalization [13]. One year after the implementation of the protocol activities, VCs achieved among these patients had increased tenfold compared to 2013 (from 5.7% to 66.7%). Time from the splenectomy procedure to the beginning of the vaccination protocol also markedly decreased (from 84.7 days in 2013 to 7.5 days after the implementation of the protocol) [13]. During the subsequent years, this protocol was promoted to other major hospitals in Apulia region. In this context, this study aimed to estimate VCs for recommended vaccinations among splenectomized patients in Apulia.

METHODS

Study design and setting

This is a retrospective observational study. The study population was identified via the Apulian regional archive of hospital discharge forms (SDO), an online database containing all information regarding hospital and inpatient procedures carried out in the whole region [14]. We considered all records referring to splenectomy using the ICD9 code 41.5, and extended our search to all

procedures performed from 2015 throughout 2020. Only subjects living in Apulia were considered. The following pieces of information were extracted: age at hospitalization, diagnosis at hospitalization, length of hospital stay, and discharge mode.

Lists of deceased Apulian inhabitants (2015-2022) were checked using the Edotto platform (Exprivia, Apulia, Italy) of the Apulian Health Information System [15]. The vaccination status of asplenic patients was assessed using the Regional Immunization Database (GIAVA) [15]. GIAVA is a digital vaccination registry containing information on the vaccination history of every Apulian inhabitant.

These three datasets were extracted and matched using the patients' unique identification numbers (PINs).

The final dataset was built as an Excel spreadsheet that integrated info on sex, age at splenectomy, characteristics of hospitalization, modality of splenectomy (elective or emergency surgery), death (YES/NO), vaccine prophylaxis (YES/NO) and the type of vaccine. An anonymized data analysis was performed using the STATA MP17 software.

The vaccination status for anti-pneumococcal, anti-*Haemophilus influenzae* type b, anti-*Neisseria meningitidis* ACYW135, anti-*Neisseria meningitidis* B, and anti-influenza (1 dose every year, in October/December), considering only subjects surviving for at least 15 days after the surgery, was evaluated. In order to define a subject as fully immunized, we considered completion of CDC guidelines as the definition of optimal immunization status [5].

Statistical analysis

Continuous variables were reported as the mean ± standard deviation and range or median and interquartile range (IQR), and categorical variables as proportions.

To analyse the determinants of anti-pneumococcal, anti-*Haemophilus influenzae* type b, anti-*Neisseria meningitidis* ACYW135, anti-*Neisseria meningitidis* B, and anti-influenza (a flu vaccine

before each flu season that followed the splenectomy) vaccines uptake (YES/NO) a multivariate logistic regression model was built for each outcome; sex (male vs. female), age at splenectomy (years), length of hospitalization (days) and cause of splenectomy (trauma vs. other) were used as determinants. The adjusted Odds Ratios (aOR) were calculated, as well as 95% Confidence Intervals (95%Cis).

For all tests, a two-sided p-value<0.05 was considered an indicator of statistical significance.

Patient and public involvement

None.

RESULTS

Since 2015, 1,650 subjects living in Apulia have undergone splenectomy; 1,576 of them (95.5%) were still alive 15 days after the surgery (Figure 1).

923 patients (58.6%) were male and the mean age at splenectomy was 55.9±20.9 years (range: 4-95); 390 out of 1.576 patients (24.7%) reported at least one chronic condition.

Most splenectomies were performed in urgency (n=941; 59.7%), while 635 surgeries (40.3%) had been previously planned; 581 out of 941 urgent splenectomies (61.7%) were required due to traumatic injuries. The median length of hospitalization was 12 days (IQR=7-20), and most patients were discharged (n=1.390; 88.2%).

VCs of recommended immunization prophylaxis per year of splenectomy are reported in Table 1; only 343 (21.1%) subjects received the seasonal flu shot before each influenza season that followed splenectomy.

Table 1. Vaccine coverage (%) per immunization prophylaxis and year of splenectomy

Year of splenectomy	Anti-meningococcal B (2 doses)	Anti-meningococcal ACYW135 (2 doses)	Anti-pneumococcal (PCV13 + PSSV23)	Anti-Hib	Seasonal flu shot*
2015 (n=272)	46 (16.9%)	39 (14.3%)	41 (15.1%)	53 (19.5%)	104 (38.2%)
2016 (n=271)	71 (26.2%)	63 (23.3%)	67 (24.7%)	72 (26.6%)	114 (42.1%)
2017 (n=276)	80 (29.0%)	66 (23.9%)	59 (21.4%)	112 (40.6%)	122 (44.2%)
2018 (n=288)	105 (36.5%)	94 (32.6%)	88 (30.6%)	84 (29.2%)	152 (52.8%)
2019 (n=241)	107 (44.4%)	98 (40.7%)	91 (37.8%)	60 (24.9%)	150 (62.2%)
2020 (n=228)	78 (34.2%)	77 (33.8%)	79 (34.7%)	94 (41.2%)	133 (58.3%)
Total (n=1.576)	487 (30.9%)	437 (27.7%)	425 (27.0%)	475 (30.1%)	775 (49.2%)

*At least one seasonal flu vaccine after splenectomy.

Only 376 patients (23.9%) got their flu shot before all influenza seasons after undergoing splenectomy. None of the subjects splenectomized in 2015 and 2016 received the recommended MenACYW$_{135}$ and PSSV23 booster doses 5 years after completing the basal cycles.

The VC of recommended vaccines per age class is described in Table 2.

Table 2. Vaccine coverage (%) per immunization prophylaxis and age class of patients

Age class (years)	Anti-meningococcal B (2 doses)	Anti-meningococcal ACYW135 (2 doses)	Anti-pneumococcal (PCV13 + PSSV23)	Anti-Hib	Seasonal flu vaccine*

0-17 (n=77)	39 (50.7%)	32 (41.6%)	16 (20.8%)	30 (39.0%)	37 (48.1%)
18-64 (n=812)	288 (35.5%)	273 (33.6%)	254 (31.3%)	282 (34.7%)	396 (48.8%)
65+ (n=687)	160 (23.3%)	132 (19.2%)	155 (22.6%)	163 (23.7%)	342 (49.8%)

*At least one seasonal flu shot after splenectomy.

The results of multivariate logistic analyses are reported in Table S1.

The median time from surgery to the first vaccine dose was 38 days (IQR=9-100) for anti-MenB, 33 (IQR=8-73) for anti-MenACYW135, 17 (IQR=6-47) for anti-PCV13, and 26 (IQR=19-67) for anti-Hib.

445 out of 1.576 patients (28.2%) died after hospital discharge, with a median time from surgery to death equal to 356 days (IQR=91-825).

DISCUSSION

The results of our study highlight low VCs in Apulian splenectomized patients. All VCs are lower than those reported in a 2020 global-level meta-analysis [12], except for the anti-menB vaccine, for which VCs are over twice as high as those reported in the literature (13% vs. 31%) [12]. Despite these unsatisfying values, an improvement was observed over the years, with an increasing trend starting from 2015 for all vaccines. The slight decrease in 2020 was likely related to the scarcity of both economic and human resources during the first stage of the COVID-19 pandemic [16].

Stratifying VCs by age group, younger subjects had higher coverages than over-65 patients. Only the anti-influenza vaccine had a similar uptake in all three age classes; this is also confirmed by our multivariate models, which evidenced an inverse correlation between age and prophylaxis (except for anti-pneumococcal vaccination). The values found in minors can be explained by habit:

most recommended vaccines are already part of the Italian infant vaccination routine, and physicians are therefore more familiar with these products when children are concerned. On the other hand, VCs in the elderly are worrisome; considering the anti-pneumococcal vaccine, which in Italy is recommended in subjects over 65 years regardless of health conditions, such low values are even more of an issue, as they suggest low levels of compliance of both patients and HCWs.

Functional and anatomical asplenia increase susceptibility to infectious diseases, especially in the elderly [17,18]. Low VCs are probably related to a misperception of risk by general practitioners and/or specialized branch physicians. These professionals may identify possible adverse events following immunization as critical risks for vulnerable patients, for whom infections are significantly worse in terms of morbidity and mortality [18].

Time from surgery to the start of vaccination is also longer than desirable: the first days after surgery are characterized by an especially high risk of infections. Although a lack of clinical evidence for the effectiveness of vaccination in splenectomized individuals is reported in the literature and no ideal timings have been defined [19], clinical experience suggests that vaccination protocols should be initiated as soon as possible. Such practice is justified by the latency time required for vaccines to elicit an effective immune response, which for most products is about 20-25 days. Clinical conditions of the patient are to be taken into consideration, as existing evidence recommends administering vaccines only after stabilization of the clinical frame. Moreover, our multivariate analyses showed that a shorter hospital stay is related to higher VCs; this observation is likely related to a tendency of physicians not to vaccinate patients with multiple comorbidities, and therefore perceived as frailer. Subjects requiring shorter hospital stays are generally easier to treat and are therefore perceived as safer targets for vaccination. Surprisingly, splenectomies caused by malignancies seem to be associated with a better uptake of MenACYW135 vaccine; this could be a statistical artifact, and more investigation is needed to clarify this point.

The strengths of our study are the long study period (6 years) and the large population we addressed; to our knowledge, only a few studies in scientific literature investigated this phenomenon on such large samples and over so many years. However, we were unable to evaluate the correlation between VCs and community care determinants. Moreover, the Edotto platform is built for administrative and non-epidemiological purposes, so there is a theoretical risk of bias; this risk is low, considering that all the healthcare information data in Apulia are digitized, and therefore our methodology is not affected by this issue. Finally, there is a theoretical risk that splenectomized subjects may have changed Region or country after the surgery, and therefore we could not record the vaccinations eventually administered.

A 2021 review identified the lack of skilled HCWs in the field of vaccinology and the unsatisfactory information available for patients, including educational materials, on the importance of vaccination for those with asplenia as two of the major determinants of low vaccination uptake [12]. The training of healthcare personnel might consist of specific courses, workshops, and events specifically designed for HCWs involved in the management of the asplenic patient (surgeons, vaccinologists, GPs). These efforts would benefit not HCWs, but also patients and their caregivers, who would be better informed regarding infections in asplenic individuals.

A multifactorial approach should be implemented to achieve high immunization coverage in this population at risk. The introduction of intra-hospital vaccination protocols for chronic patients has been shown to strongly increase the VC (up to 10-fold) of these individuals [13] and to guarantee good adherence to prophylaxis recommendations in the years following the splenectomy [20]. When it is not possible to vaccinate in a hospital setting, cooperation between the vaccinologist, physicians from other specialties, and GPs seems to be a determining factor for achieving higher immunization rates in these patients. Currently, the lack of recommendations by GPs and the absence of a clear communication circuit between GPs and branch specialists are considered the

main obstacles to these patients' access to immunization. A 2020 French study [21] reported low VCs in a sample of 103 patients splenectomized from 2013 to 2016, concluding that the role of GPs is central in the long-term monitoring and management of infections in this population of patients, in collaboration with all healthcare professionals.

At the same time, educating patients about their health conditions and the associated risks is crucial [22]. The proposals for improving VCs differed among various experiences in literature, ranging from the use of bracelets to medical records to spleen registries; nevertheless, none of these strategies were reported as sufficiently structured or contextualized to improve the overall management of asplenic patients [12].

In conclusion, VCs in Apulian splenectomized patients are sub-optimal, in line with the values reported in scientific literature for other populations worldwide. The direct consequence of these low VCs is that hundreds of patients are at risk of developing severe vaccine-preventable diseases. Public health institutions need to enforce new approaches aimed at increasing vaccination aptitude in this population, implementing educational measures for patients and families, education for GPs and specialists, and ad hoc communication campaigns. The integration between hospital and community care appears to be fundamental for achieving the goal of protecting this high-risk population. In the future new techniques and scientific innovations, such as the experimental reinfusion of splenic lymphocytes in splenectomized patients [23], could help to reduce the morbidity and mortality in asplenic subjects; till then the vaccination prophylaxis of splenectomized subjects is the main preventive tool to avoid infectious' complications in these patients.

Funding

This research was funded by the Apulia Regional Observatory of Epidemiology (grant number N/A).

Competing interests

The authors declare that they have no competing interests.

Data availability statement

The dataset is not available due to privacy restrictions.

Ethics approval

The present study did not require ethical approval for its observational design according to Italian law (Gazzetta Ufficiale no. 76 dated March 3, 2008). The study was carried out in accordance with the Declaration of Helsinki.

Contributors

FPB contributed to the design of the study, data analysis, and the drafting of the manuscript. PS and ADL contributed to the design of the study. EC contributed to data collection and analysis. ST and CAG contributed to the revision of the study protocol and the manuscript. The corresponding author attests that all authors listed meet the criteria for authorship and that no others meeting the criteria have been omitted. All authors have read and approved the manuscript.

REFERENCES

1. Bonanni P, Grazzini M, Niccolai G, et al. Recommended vaccinations for asplenic and hyposplenic adult patients. Hum Vaccin Immunother. 2017;13(2):359–368. .
2. Chong J, Jones P, Spelman D, et al. Overwhelming post-splenectomy sepsis in patients with asplenia and hyposplenia: a retrospective cohort study. Epidemiol Infect. 2017;145(2):397–400.
3. Waghorn DJ. Overwhelming infection in asplenic patients: current best practice preventive measures are not being followed. J Clin Pathol. 2001;54(3):214–218.
4. Sciberras S. Preventing severe infection after splenectomy: what about old splenectomies? BMJ. 2005;331(7516):576.
5. CDC. Asplenia and adult vaccination. [accessed on 2020 Aug 1]. Available on: https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/asplenia.html#:~:text=Asplenia%20and%20Adult%20Vaccination%26text=Tdap%20vaccine%20to%20protect%20against,pneumonia%20and%20other%20pneumococcal%20disease.Last
6. Castagnola E, Fioredda F. Prevention of life-threatening infections due to encapsulated bacteria in children with hyposplenia or asplenia: a brief review of current recommendations for practical purposes. Eur J Haematol. 2003;71(5):319–326.
7. Howdieshell TR, Heffernan D, Dipiro JT. Therapeutic agents committee of the surgical infection society. surgical infection society guidelines for vaccination after traumatic injury. Surg Infect (Larchmt). 2006;7(3):275–303.
8. Martinón-Torres F, Bernatowska E, Shcherbina A, et al. Meningococcal B vaccine immunogenicity in children with defects in complement and splenic function. Pediatrics. 2018;142(3):e20174250. [published correction appears in Pediatrics. 2019 Mar;143(3):]

9. Forstner C, Plefka S, Tobudic S, et al. Effectiveness and immunogenicity of pneumococcal vaccination in splenectomized and functionally asplenic patients. Vaccine. 2012;30(37):5449–5452.
10. Spoulou V, Tzanakaki G, Lekka S, et al. Natural and vaccine-induced immunity to neisseria meningitidis serogroup C in asplenic patients with β-thalassemia. Vaccine. 2011;29(27):4435–4438.
11. Uslu A, Yetiş H, Aykas A, et al. The efficacy and immunogenicity of pneumo-23 and ACT-HIB in patients undergoing splenectomy. . Ulusal travma ve acil cerrahi dergisi = Turkish journal of trauma & emergency surgery. TJTES. 2006;12(4):277–281.
12. Bianchi FP, Stefanizzi P, Spinelli G, Mascipinto S, Tafuri S. Immunization coverage among asplenic patients and strategies to increase vaccination compliance: a systematic review and meta-analysis. Expert Rev Vaccines. 2021 Mar;20(3):297-308.
13. Gallone MS, Martino C, Quarto M, Tafuri S; Bari Policlinico General Hospital. Active offer of vaccinations during hospitalization improves coverage among splenectomized patients: An Italian experience. Am J Infect Control. 2017 Aug 1;45(8):e87-e89.
14. Bianchi FP, Gallone MS, Fortunato F, Boccalini S, Martinelli D, Prato R, Tafuri S. Epidemiology and cost of cervical cancer care and prevention in Apulia (Italy), 2007/2016. Ann Ig. 2018 Nov-Dec;30(6):490-501.
15. Pedote PD, Termite S, Gigliobianco A, Lopalco PL, Bianchi FP. Influenza Vaccination and Health Outcomes in COVID-19 Patients: A Retrospective Cohort Study. Vaccines (Basel). 2021 Apr 8;9(4):358.
16. Deana C, Rovida S, Orso D, et al. Learning from the Italian experience during COVID-19 pandemic waves: be prepared and mind some crucial aspects. *Acta Biomed*. 2021;92(2):e2021097. Published 2021 May 12.

17. Squire JD, Sher M. Asplenia and Hyposplenism: An Underrecognized Immune Deficiency. Immunol Allergy Clin North Am. 2020 Aug;40(3):471-483.

18. Bianchi FP, Tafuri S. Vaccination of Elderly People Affected by Chronic Diseases: A Challenge for Public Health. Vaccines (Basel). 2022 Apr 19;10(5):641.

19. Lenzing E, Rezahosseini O, Burgdorf SK, Nielsen SD, Harboe ZB. Efficacy, immunogenicity, and evidence for best-timing of pneumococcal vaccination in splenectomized adults: a systematic review. Expert Rev Vaccines. 2022 May;21(5):723-733.

20. Bianchi FP, Rizzo LA, De Nitto S, Stefanizzi P, Tafuri S. Influenza vaccination coverage among splenectomized patients: an Italian study on the role of active recall in the vaccination compliance. Hum Vaccin Immunother. 2019;15(11):2644-2649.

21. Quéffélec C, Billet L, Duffau P, Lazaro E, Machelart I, Greib C, Viallard JF, Pellegrin JL, Rivière E. Prevention of infection in asplenic adult patients by general practitioners in France between 2013 and 2016 : Care for the asplenic patient in general practice. BMC Fam Pract. 2020 Aug 12;21(1):163.

22. Gonzalez RA, Robbins JM, Garwe T, Stewart KE, Sarwar Z, Cross AM, Celii AM, Albrecht RM. Effect of Post-splenectomy Booster Vaccine Program on Vaccination Compliance in Trauma Patients. Am Surg. 2021 May;87(5):796-804.

23. Li SC, Kabeer MH. Autologous Splenocyte Reinfusion Improves Antibody-Mediated Immune Response to the 23-Valent Pneumococcal Polysaccharide-Based Vaccine in Splenectomized Mice. Biomolecules. 2020 May 1;10(5):704.

Figure 1. Flowchart of computation of final sample size

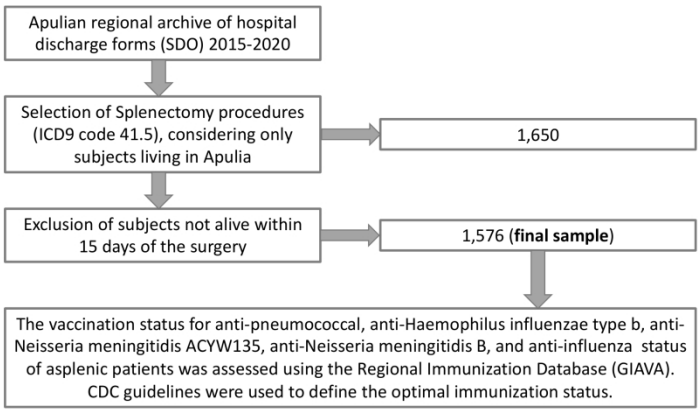

Figure 1. Flowchart of computation of final sample size.

857x482mm (79 x 79 DPI)

Table S1. Analysis of determinants of anti-pneumococcal, anti-*Haemophilus influenzae* type b, anti-*Neisseria meningitidis* ACYW135, anti-*Neisseria meningitidis* B, and influenza vaccines uptake (YES/NO) through multivariate logistic regression models.

Determinant	Anti-MenB		Anti-MenACYW135		Anti-pneumo		Anti-Hib		Flu vaccine*	
	aOR (95%CI)	p-value	aOR (95%CI)	p-value	aOR (95%CI)	p-value	aOR (95%CI)	p-value	aOR (95%CI)	p-value
Sex (male vs. female)	1.05 (0.84-1.32)	0.666	1.09 (0.86-1.38)	0.480	1.11 (0.88-1.41)	0.366	0.93 (0.74-1.17)	0.548	0.91 (0.70-1.17)	0.454
Age at splenectomy (yrs)	0.98 (0.97-0.99)	<0.0001	0.99 (0.97-0.99)	<0.0001	1.00 (0.99-1.00)	0.434	0.99 (0.98-0.99)	<0.0001	1.01 (0.99-1,01)	0.084
Length of hospitalization	0.98 (0.97-0.99)	<0.0001	0.98 (0.97-0.99)	<0.0001	0.97 (0.96-0.98)	<0.0001	0.99 (0.98-0.99)	0.002	0.98 (0.97-0.99)	0.001
Cause of splenectomy (trauma vs. other)	0.84 (0.65-1.09)	0.185	0.76 (0.56-0.99)	0.040	0.92 (0.70-1.19)	0.509	1.06 (0.82-1.36)	0.665	1.05 (0.80-1.40)	0.716

***a flu shot before each flu season that followed the splenectomy**

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	5-6

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7-11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-11
		(*b*) Report category boundaries when continuous variables were categorized	7-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.