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

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

INTRODUCTION

Splenectomised/asplenic patients have a 10–50 fold higher risk than the general population of developing overwhelming postsplenectomy infection (OPSI) caused by encapsulated bacteria such as Streptococcus pneumoniae (>50% of cases), Haemophilus influenzae type b (Hib) and Neisseria meningitidis1,2; 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 immunisation schedule, in compliance with international vaccination guidelines5; indeed, the US 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-PCV (PPSV23) 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 (two or
three doses, depending on the employed vaccine), the anti-influenza vaccination (one dose every fall, before the start of the influenza season), the anti-tetanus-diphtheria-acellular pertussis vaccine booster and the anti-Varicella Zoster Virus vaccine. 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 and anti-varicella vaccines should, therefore, be taken into consideration when first visiting an asplenic patient.

Guidelines have been updated over the years, and many studies 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 showed a 55.1% (95% CI 41.0% to 69.2%) anti-pneumococcal VC, a 48.3% (95% CI 34.3% to 62.3%) VC for anti-Hib, a 33.7% (95% CI 23.6% to 43.9%) VC for anti-Neisseria meningitidis C/ACYW135, a 13.3% (95% CI 7.0% to 19.5%) VC for anti-Neisseria meningitidis B and a 53.2% (95% CI 22.0% to 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 postsplenectomy patients.

In 2014, Bari Policlinico General Hospital (Apulia, Southern Italy, ~400,000 inhabitants) approved a specific protocol for actively offering vaccinations to splenectomised patients during their hospitalisation. One year after the implementation of the protocol activities, VCs achieved among these patients had increased 10-fold compared with 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). 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 splenectomised 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. We considered all records referring to splenectomy using the International Classification of Diseases, 9th revision (ICD9) code 41.5, and extended our search to all procedures performed from 2015 to 2020. Only subjects living in Apulia were considered. The following pieces of information were extracted: age at hospitalisation, diagnosis at hospitalisation, 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. The vaccination status of asplenic patients was assessed using the Regional Immunisation Database (GIAVA). 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.

The final dataset was built as an Excel spreadsheet that integrated info on sex, age at splenectomy, characteristics of hospitalisation, modality of splenectomy (elective or emergency surgery), death (YES/NO), vaccine prophylaxis (YES/NO) and the type of vaccine. An anonymised data analysis was performed using the STATATA MP V.17 software.

The vaccination status for anti-pneumococcal, anti-Haemophilus influenzae type b, anti-Neisseria meningitidis ACYW135, anti-Neisseria meningitidis B and anti-influenza (one 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 immunised, we considered completion of CDC guidelines as the definition of optimal immunisation status.

Statistical analysis
Continuous variables were reported as the mean±SD and range or median and 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 influenza vaccine before each influenza 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 hospitalisation (days) and cause of splenectomy (trauma vs other) were used as determinants. The adjusted ORs were calculated, as well as 95% CIs.

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

Patient and public involvement
None.

RESULTS
Since 2015, 1650 subjects living in Apulia have undergone splenectomy; 1576 of them (95.5%) were still alive 15 days after the surgery (figure 1).

A total of 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 hospitalisation was 12 days (IQR=7–20), and most patients were discharged (n=1,390; 88.2%).

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

Only 376 patients (23.9%) got their influenza shot before all influenza seasons after undergoing splenectomy. None of the subjects splenectomised in 2015 and 2016 received the recommended MenACYW135 and PPSV23 booster doses 5 years after completing the basal cycles.

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

The results of multivariate logistic analyses are reported in online supplemental 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.

A total of 445 out of 1576 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 splenectomised 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-PCV, 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 (GPs) and/or specialised branch physicians. These professionals may identify possible adverse events following immunisation 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 characterised by an especially high risk of infections. Although a lack of clinical evidence for the effectiveness of vaccination in splenectomised individuals is reported...
in the literature and no ideal timings have been defined, 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 stabilisation 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 artefact, 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 digitised, and therefore, our methodology is not affected by this issue. Finally, there is a theoretical risk that splenectomised 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. 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 immunisation coverage in this population at risk. The introduction of intrahospital vaccination protocols for chronic patients has been shown to strongly increase the VC (up to 10-fold) of these individuals and to guarantee good adherence to prophylaxis recommendations in the years following the splenectomy. 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 immunisation 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 immunisation. A 2020 French study reported low VCs in a sample of 103 patients splenectomised 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. 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 contextualised to improve the overall management of asplenic patients.

In conclusion, VCs in Apulian splenectomised patients are suboptimal, 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 splenectomised patients, could help to reduce the morbidity and mortality in asplenic subjects; till then the vaccination prophylaxis

<table>
<thead>
<tr>
<th>Age class (years)</th>
<th>Anti-meningococcal B (2 doses)</th>
<th>Anti-meningococcal ACYW135 (2 doses)</th>
<th>Anti-pneumococcal PCV13+PPSV23</th>
<th>Anti-Hib</th>
<th>Seasonal influenza vaccine*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–17 (n=77)</td>
<td>39 (50.7%)</td>
<td>32 (41.6%)</td>
<td>16 (20.8%)</td>
<td>30 (39.0%)</td>
<td>37 (48.1%)</td>
</tr>
<tr>
<td>18–64 (n=812)</td>
<td>288 (35.5%)</td>
<td>273 (33.6%)</td>
<td>254 (31.3%)</td>
<td>282 (34.7%)</td>
<td>396 (48.8%)</td>
</tr>
<tr>
<td>65+ (n=687)</td>
<td>160 (23.3%)</td>
<td>132 (19.2%)</td>
<td>155 (22.6%)</td>
<td>163 (23.7%)</td>
<td>342 (49.8%)</td>
</tr>
</tbody>
</table>

*At least one seasonal influenza shot after splenectomy.

PCV13, 13-valent conjugate anti-pneumococcal vaccine; PPSV23, 23-valent polysaccharide anti-pneumococcal vaccine.
of splenectomised subjects is the main preventive tool to avoid infectious’ complications in these patients.

**Contributors** FPB designed the study, analysed 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. ST was the guarantor. The corresponding author attests that all authors listed met the criteria for authorship and that no others meeting the criteria have been omitted. All authors have read and approved the manuscript.

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

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**ORCID iD** Silvio Tafuri http://orcid.org/0000-0003-4194-0210

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