Received: 15 December 2023 | Accepted: 15 February 2024

DOI: 10.1111/bjh.19361

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

GUIDELINE

BSH Guideline

Prevention and treatment of infection in patients with an absent or hypofunctional spleen: A British Society for Haematology guideline

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Summary

Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen were published by the British Committee for Standards in Haematology in 1996 and updated in 2002 and 2011. With advances in vaccinations and changes in patterns of infection, the guidelines required updating. Key aspects included in this guideline are the identification of patients at risk of infection, patient education and information and immunisation schedules. This guideline does not address the non-infective complications of splenectomy or functional hyposplenism (FH). This replaces previous guidelines and significantly revises the recommendations related to immunisation. Patients at risk include those who have undergone surgical removal of the spleen, including partial splenectomy and splenic embolisation, and those with medical conditions that predispose to FH. Immunisations should include those against *Streptococcus pneumoniae* (pneumococcus), *Neisseria meningitidis* (meningococcus) and influenza. *Haemophilus influenzae* type b (Hib) is part of the infant immunisation schedule and is no longer required for older hyposplenic patients. Treatment of suspected or proven infections should be based on local protocols and consider relevant anti-microbial resistance patterns. The education of patients and their medical practitioners is essential, particularly in relation to the risk of serious infection and its prevention. Further research is required to establish the effectiveness of vaccinations in hyposplenic patients; infective episodes should be regularly audited. There is no single group ideally placed to conduct audits into complications arising from hyposplenism, highlighting a need for a national registry, as has proved very successful in Australia or alternatively, the establishment of appropriate multidisciplinary networks.

KEYWORDS

antibiotic(s), asplenia, hyposplenism, infection, partial splenectomy, registry, splenectomy, splenic embolisation, vaccination

KEY RECOMMENDATIONS

These recommendations are tailored for UK practitioners. Those from other countries may need to evaluate their respective vaccination guidelines depending on local infection patterns and immunisation schedules.

- **Patients should be provided with appropriate written and/or electronic information and carry a card to alert healthcare professionals to the risk of overwhelming infection (Grade 1A). Patients may wish to invest in an alert pendant or bracelet. Information is available online (updated March 2022)** https://www.gov.uk/government/publicatio

ns/splenectomy-leaflet-and-card/information-for-patients-with-an-absent-or-dysfunctional-spleen.

- **Patients should be educated about the potential risks of overseas travel, particularly with regards to malaria and unusual infections such as those associated with animal bites (Grade 1B).**
- **Patient records should be clearly labelled to indicate their underlying increased risk of serious infection. Up-to-date vaccination and re-vaccination status should be clearly and adequately documented, with particular emphasis on documenting vaccines that have been administered in non-primary care settings (Grade 1A).**
- **Local health care providers should maintain and regularly update a register of at-risk patients. Ideally, a national splenectomy registry should be established. A pilot audit using the data already present in the national primary care sentinel network database, which covers a third of the population, would be a useful starting point (Grade 2C).**
- **Vaccinations: splenectomised patients and those with functional hyposplenism (FH) should receive vaccines against pneumococcus (Grade 1A) and meningococcus, as well as annual influenza immunisation (Grade 1A). The 23-valent pneumococcal polysaccharide vaccine (PPV23) should be offered from 2 years of age (Grade 1B), with PPV23 boosters offered every 5 years (Grade 1B). With Hib vaccination administered as part of the national infant immunisation schedule, Hib vaccination is no longer recommended for older hyposplenic individuals (Grade 1B). The incidence of invasive Hib disease is very low in the UK as a result of herd protection from the childhood programme introduced in 1992 and updated in 2006. Meningococcal ACWY conjugate vaccine boosters are also not recommended because of the very low disease incidence from these serotypes due to the herd protection offered by the adolescent MenACWY conjugate vaccine programme since 2015 in the UK (Grade 1C). Patients also receive the COVID-19 vaccination according to national recommendations (Grade 1C).**
- **Lifelong prophylactic antibiotics, using oral penicillins or macrolides, should be offered to patients considered to be at continued high risk of pneumococcal infection (Grade 1B). This advice should be regularly reviewed in the light of local antibiotic resistance patterns.**
- **Patients not at high risk should be counselled regarding the available evidence for the risks and benefits of lifelong antibiotics and may choose to discontinue them (Grade 2C).**
- **All patients should carry a supply of appropriate rescue antibiotics for emergency use (Grade 1A).**
- **Patients developing infection, despite the above measures, must be given parenteral antibiotics and admitted urgently to hospital (Grade 1A).**

METHODOLOGY

Guidelines for prevention and treatment of infection in patients with an absent or hypofunctional spleen were published in 1996 [1] and subsequently updated. [2] Recent updates in immunisation required that the guidelines be updated.[3] This guideline was compiled according to the British Society for Haematology (BSH) process at https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found in appendix 3 of the BSH guidelines process at http://www.gradeworkinggroup.org. Members of the writing group were selected to be representative of UK-based medical practice. The writing group wish to acknowledge additional input into the guidelines provided by discussion with the UK Health Security Agency (UKHSA) and the Royal College of General Practitioners (RCGP) through its Research and Surveillance Centre (RSC).[4]

Literature review details

The literature search for this guideline was carried out using the online search engine Medline (PubMed). The first search was performed in May 2022 and updated in June 2023. The three searches carried out were:

- (antibiotic OR antibiotics) AND (splenectomy OR partial splenectomy OR asplenia OR asplenic OR hyposplenism OR splenic embolisation OR splenic embolisation OR splenic embolism)
- (infection OR infections) AND (splenectomy OR partial splenectomy OR asplenia OR asplenic OR hyposplenism OR splenic embolisation OR splenic embolisation OR splenic embolism)
- (vaccine OR vaccination OR immunisation) AND (splenectomy OR partial splenectomy OR asplenia OR asplenic OR hyposplenism OR splenic embolisation OR splenic embolisation OR splenic embolism)

Filters were applied to include publications written in English, publications with abstracts and publications of studies conducted in humans. Additionally, only publications reporting clinical trials, guidelines, meta-analyses and systematic reviews were included. The search results included publications between January 01 2011 and June 21 2023. These search criteria returned a total of 599 results, which were manually reviewed.

Review of the manuscript

The review of the manuscript was performed by the BSH Guidelines Committee General Haematology Task Force, the

BSH Guidelines Committee and the sounding board of the BSH. It was also on the members section of the BSH website for comment. It has also been reviewed by representatives of the RCGP and members of the Immune Thrombocytopenia (ITP) Support Association who have had splenectomy; these organisations do not necessarily approve or endorse the contents.

INTRODUCTION

The spleen plays a crucial role in regulating immune homeostasis as it links innate and adaptive immunity. The spleen functions as a phagocytic filter that removes senescent and damaged cells (culling), solid particles from the cytoplasm of erythrocytes (pitting) and opsonised blood-borne microorganisms. It also produces pentameric natural IgM antibodies by memory B cells that facilitate phagocytosis by splenic macrophages. In this guideline, the term 'hyposplenism' refers to any person with asplenia or reduced splenic function.

Functional hyposplenism, impairment of splenic function, is an acquired disorder caused by several haematological and immunological diseases, whereas asplenia refers to the absence of the spleen, which is mostly postsurgical and rarely congenital.[5–7]

Overwhelming infections caused by encapsulated bacteria have a high mortality, a fulminant course, and are refractory to common treatments; therefore, prevention through vaccination and antibiotic prophylaxis is the basis of the management of patients who have had splenectomy or have FH. Antibiotic prophylaxis is key since current vaccines cannot cover all serotypes of pneumococcus or all strains of meningococcus.

While there is general advice about education in this guideline, the treatment and vaccination recommendations are age-specific.

Causes of asplenia and hyposplenism

Asplenia may be congenital or acquired when the spleen has been removed surgically, especially after road traffic accidents. Congenital asplenia may be identified incidentally during routine abdominal ultrasound examination or when unexpected Howell–Jolly bodies are seen on the blood film, or as part of an investigation after a serious infection. It is important to look for these bodies on a blood film, as their presence is characteristic of splenic hypofunction. Splenic function is also lost when the spleen has atrophied following splenic artery thrombosis, therapeutic splenic embolisation or repeated infarction (auto-splenectomy), as seen in sickle cell disease or autoimmune diseases such as anti-phospholipid syndrome, lupus or rheumatoid arthritis. FH is physiological in neonates and the elderly and pathological when the spleen is congested with blood (e.g. malaria, splenic vein thrombosis, portal hypertension, primary pulmonary hypertension), infiltrated (amyloidosis, sarcoidosis, metastasis, lymphoma, myeloproliferative neoplasms or Gaucher disease) or contains large cysts or haemangiomas. It also occurs in a wide range of medical conditions,[8] including following stem cell transplantation, and should be considered in children with unexplained thrombocytosis or recurrent infections.[9]

Identification of patients with asplenia or FH is important because simple measures such as vaccination against common pathogens (e.g. *Streptococcus pneumoniae*, *Neisseria meningitidis*, influenza and SARS-CoV-2) and antibiotics diminish the frequency and gravity of the infections in this high-risk group.

Severity of hyposplenism

Several diseases or conditions can be complicated by splenic hypofunction, ranging from mild hyposplenism to splenic atrophy.[5] There is no easy and reliable diagnostic method to assess its presence and severity (Table 1).

Diagnosis of hyposplenism

The presence of Howell–Jolly bodies (nuclear remnants) is considered an indicator of splenic hypofunction,[10] and these

TABLE 1 Diagnostic techniques for functional hyposplenism (FH) (adapted from Ref [99]).

Test	Description	Comments	References
Detection of Howell–Jolly bodies on peripheral blood film	Nuclear remnants in erythrocytes (appear as basophilic purple spot)	No need for special equipment, inaccurate in assessing severity	[13]
Detection of pitted erythrocytes by phase contrast microscopy	Erythrocytes with membrane indentations—Gold standard 4% is upper limit of normal range	Requires phase contrast microscope and expertise, correlates well with severity and radioisotopic methods	[100]
Spleen scintigraphy with technetium-99m-labelled sulphur colloid	Quantitation of splenic uptake of colloidal sulphur particles enables a fairly accurate static assessment of spleen function	Uptake is lower in FH and is proportional to severity. Hypertrophy of the left hepatic lobe could interfere with reading	[101]
Technetium-99m-labelled or rubidium-81-labelled heat-damaged autologous erythrocyte clearance	Measurement of clearance time allows a dynamic evaluation of spleen function	Not suitable for clinical practice—false positive or negative in relation to variable degree of heat damage, difficult tests	[102]
Flow cytometry for IgM+ Cd27+ B cells	Evaluation of a specific subset	Easily available blood test	[98]

may be seen after partial splenic embolisation.[11] Other red cell abnormalities observed in the peripheral blood film in patients with hyposplenism include acanthocytes (spur cells), target cells, haemoglobin precipitates (Heinz bodies) and iron granules (Pappenheimer bodies). Leucocytosis (lymphocytosis and monocytosis), along with thrombocytosis, usually develops postsplenectomy and in other hyposplenism and may provide clues to the diagnosis of an occult underlying disease.[12]

The incidental finding of a small spleen during abdominal imaging should prompt appropriate tests for quantitation of splenic function, such as examination of a peripheral blood film for Howell–Jolly bodies.[13]

EDUCATION AND INFORMATION

It is essential to educate hyposplenic and asplenic patients and their families about the risk of severe infection, particularly with encapsulated organisms, as well as the importance of prompt recognition and treatment of infection to avoid death from overwhelming postsplenectomy sepsis (OPSI). A study of more than 8000 splenectomised USA veterans who were followed up for up to 27 years found that the increased risks for sepsis and thrombosis persisted long term.[14]

The education of medical personnel is essential. The perisplenectomy vaccination rate may be improved by the introduction of a pharmacy-driven kit.[15,16] Patients are not always followed up in hospital, particularly when their underlying condition is rendered asymptomatic following splenectomy (e.g. hereditary spherocytosis or immune thrombocytopenia). From this point onwards the primary care physician should take responsibility for ongoing care and vaccinations. A study from the Netherlands noted barriers to good practice included a lack of clarity about which physicians had responsibility for vaccinations and follow-up, together with poor patient knowledge.[17] Adults who have had a splenectomy many years previously may not be aware of the risks and may never have been offered antibiotic prophylaxis or vaccination.[18] Patients splenectomised for trauma may miss initial[19] and also booster vaccinations if not followed up.[20]

Patients whose splenic rupture is treated by embolisation have variable vaccination status.[21] A multicentre review of splenic embolisation noted variation in both post-treatment antibiotic prophylaxis and immunisation, suggesting guidelines are needed.[22] Some studies suggest that immune function is preserved after splenic artery embolisation and that vaccination may not be warranted.[23,24] The vaccination rates are lower in these patients, who appear to have a lower rate of infection, but larger studies and more evidence are required.[25] Sixteen patients followed up for 4.7–12.8 years after embolisation all had evidence of IgM memory B cells, splenic tissue visible on ultrasound and no history of severe infections, further supporting the proposal that vaccinations are not mandatory.[26] However, this was a small study and measurement of IgM memory B cells is not a validated method for assessment of immune function. Decisions about vaccination in these patients should be made on an individual basis, with vaccination being considered for patients who have other reasons for immune dysfunction.

Postsplenectomy sepsis is most common in young children aged 0–2 years and in adults >60 years of age. It should be noted that the infection risk also relates to the underlying cause for splenectomy and so may be greater in some patients than others, such as patients with thalassaemia, sickle cell disease and malignancy[27] and less in those splenectomised for trauma.[28] Although the risk is highest in the first 3 years after splenectomy, OPSI has been reported to occur many decades later.[29] Patients and their relatives should be aware that, despite vaccination and prophylactic antibiotics, break-through infections may still occur, and when unwell, patients should seek and follow appropriate medical advice.

A telephone survey of 100 patients splenectomised for trauma showed initial vaccination rates of about 70% but poor revaccination rates. Only 27% of participants recalled being given education about vaccination; 91% reported that a brochure would be useful.[30] A large Italian study of 1579 splenectomised individuals (2015–2020, all causes) demonstrated that only 27%–31% had received appropriate vaccination (Meningococcal B vaccine [MenB] 30.9%, meningococcal ACWY conjugate vaccine [Men ACWY] 27.7%, pneumococcal vaccine 27%, *Haemophilus influenzae* type b vaccine [Hib] 31%). None of those splenectomised in 2015 and 2016 had received Men ACWY or the 23-valent pneumococcal polysaccharide vaccine (PPV23), emphasising the need for improved education of patients, public health and primary physicians.[31] These findings are consistent with their earlier literature review of 24 studies.[32] Similar data were reported from North America.[33] All these studies demonstrate the need for better education and management of the postsplenectomy infection risk.

Patients travelling abroad should be educated about the risks of animal bites[34] and the potential risks of tick and mosquito-borne diseases. Travel to areas where malaria is endemic carries a higher risk of severe disease compared to people with a functioning spleen, and patients should be made aware of this. People at risk need precise information about the correct chemoprophylaxis relevant to local patterns of resistance and advice about measures to reduce exposure to mosquito and tick bites.[35–37]

Patients may obtain information from the internet, but this should not be their only source. A Canadian study in 2008 reviewed information available on 89 websites on the internet, noting that 84% reported the long-term risk of infection and 79% mentioned vaccinations, but that the mean reading grade level was far above what is recommended for patient literature.[38]

Information should be offered in both written and electronic form (where available). Patients should be encouraged to wear an alert bracelet or equivalent and carry a card with information about their condition, other clinical details and contact telephone numbers. In an emergency, this information may be lifesaving. They should also have a supply of an

appropriate broad-spectrum rescue antibiotic at home to begin when a fever develops.

Education of patients and their families and participation in registries have both been shown to improve knowledge and reduce the risks of sepsis (see below).

Patient education

German researchers performed a single-centre study comparing 106 asplenic patients who received an intensive Health Action Process Approach-informed intervention[39] with a historical group of 113 patients who did not receive this input. The treated group showed a significantly higher adherence to guideline-based preventive control measures.[40] A small Canadian pilot study of a toolkit including patient information supplied as an educational booklet and a medical alert card demonstrated increased uptake of vaccinations and appropriate fever management.[41]

In France, national guidelines are published annually. Adherence by general practitioners was assessed in three hospitals and found to be insufficient.[42] Pneumococcal and meningococcal vaccine uptake was only 57%, with 74% uptake against Hib and 59% against influenza, with only 24% receiving all four vaccines. Notably, half the patients had experienced infections. Similar data have been reported from Slovenia, and these authors also recommend the establishment of a central registry for asplenic patients.[43]

Registries

The establishment of a patient splenectomy registry in Australia was shown to be cost-effective,[44] with a 69% reduction in the risk of infection among registered patients.[45] Assessment of adherence to guidelines and long-term management demonstrated that 77% had good knowledge of key educational points to reduce the chances of infection, but they were less likely to receive the most recent vaccines.[46] The majority were taking or had used antibiotic prophylaxis (70%) and had a supply of emergency antibiotics (66%). More than 12 000 patients are registered (June 2023), including 89% postsplenectomy, 6% with a non-functioning spleen and 5% previously treated by splenic artery embolisation. Guidelines have been developed for both adults and children (https://spleen.org.au/).[47] Patient and doctor education is key. The website has easy-to-follow guidelines on vaccination for both adults and children. Spleen Australia distributes 'education kits' that contain many items, including vaccination cards and alerts. Registered patients, their primary care physicians and clinic nurses are encouraged to go to the website www.spleen.org.au for the current medical recommendations and health updates. Patients are advised to keep an emergency pack of antibiotics to start when they develop a fever. The registry has provided other opportunities for research; those splenectomised for trauma are more likely to have residual splenic function, although the significance of this is unknown.[48] Other authors, including in the UK, note the benefits of and need for registries.[49–52] A UK national splenectomy registry would help to answer many questions about infection and thrombosis risks postsplenectomy.[53]

ANTI-INFECTION PROPHYLAXIS

The prevention of infection in patients without a functioning spleen has depended, and still does, depend on three major strategies:

- education of the patient as discussed above;
- the adoption of appropriate vaccination schedules;
- the use of prophylactic antibiotics, providing pneumococcal cover.

Vaccination rates in asplenic patients are not optimal; while many patients receive pneumococcal vaccine, the complete recommended schedule was received by only 6% of children with sickle cell disease in a single-centre study[54] and also reviewed in 2014.[55]

VACCINATIONS IN PATIENTS WITH ASPLENIA OR HYPOSPLENISM

Pneumococcal vaccination

Vaccinations, including live vaccines, can be given safely to children or adults with an absent or hypofunctional spleen, and vaccination against a range of potential pathogens has become an accepted practice.[3]

Hyposplenic individuals, especially young children, have a high risk of invasive infections caused by encapsulated organisms (particularly *S. pneumoniae*, Hib and *N. meningitidis*) and, at the same time, have an inherently reduced ability to mount protective antibody responses to polysaccharide antigens, which may result in vaccine failure. There are over 100 different pneumococcal serotypes that can cause invasive disease in humans. The mainstay of pneumococcal vaccination has, for many years, been the 23-valent pneumococcal polysaccharide vaccine (PPV23), which provides limited and short-term protection.[56] Despite extensive efforts, some patients may remain unvaccinated, while vaccinated individuals may develop pneumococcal disease caused by one of the vaccine serotypes, because of waning immunity, or by one of the non-vaccine serotypes.[57]

Unlike polysaccharide vaccines, covalent linkage of polysaccharide to an immunogenic carrier protein (conjugation) can significantly enhance immune protection by inducing a T-cell-dependent immune response. Conjugate vaccines are highly immunogenic in infants as young as 2 months of age, provide higher antibody titres and induce immunological memory. Since young children are the main nasopharyngeal carriers of *S. pneumoniae* and because conjugate vaccines prevent carriage acquisition, the childhood PCV

programme was associated with large declines in invasive pneumococcal disease (IPD) not only in vaccinated children but, by interrupting pneumococcal transmission, across all age groups through indirect (population) protection.[58,59] Consequently, there is currently very little pneumococcal disease due to PCV13 serotypes compared to the pre-PCV period in the UK. The implementation of both PCV7 and PCV13 was, however, associated with replacement disease caused by serotypes not included in either vaccine, with large increases in pneumococcal disease caused by non-PCV13 serotypes occurring after 2014, particularly serotypes 8, 12F and 9N, which were responsible for nearly 40% of IPD cases by 2018.[58,60] More recently, the COVID-19 pandemic, alongside large-scale lockdowns and restrictions, was associated with large declines in respiratory viral and bacterial infection, including pneumococcal disease, across all age groups since March 2020.[61] As restrictions were gradually eased, IPD cases started to increase, initially in toddlers and then in other age groups, although overall IPD incidence up to the end of 2022 remained substantially lower than prepandemic rates.[62] Reassuringly, unlike past influenza pandemics, infection with SARS-CoV-2, the virus responsible for COVID-19, was not associated with an increased risk of secondary pneumococcal infections.[63]

Recently, a 15-valent PCV (PCV15) has been approved for children and adults, as well as a 20-valent vaccine (PCV20) for adults, but as of May 2023, neither vaccine is recommended in the national UK immunisation programme.

In hyposplenic individuals, conjugate vaccines are immunogenic and have been administered safely both before and after polysaccharide vaccines.[64] Antibodies after either polysaccharide or conjugate vaccination wane with time, with evidence of more rapid waning in hyposplenic compared to healthy individuals,[65] thus warranting regular booster vaccination. At the same time, however, multiple vaccinations with PPV23, especially within 5 years, can result in attenuated antibody responses to subsequent vaccination with PCV or PPV23, resulting in serotype-specific immune hyporesponsiveness.[66] In one study, lower prebooster pneumococcal antibody levels were associated with higher postbooster pneumococcal antibody concentrations in hyposplenic patients, highlighting the need for an adequate interval between pneumococcal vaccine doses, although the optimal timing of the booster remains to be established.[66]

Tables 2 and 3 summarise current guidance for vaccination of hyposplenic individuals against the three most important encapsulated pathogens based upon the age at which hyposplenism is diagnosed.

Pneumococcal vaccination for patients with hyposplenism

It should be recognised that this is a rapidly evolving field and current advice should always be the first point of reference—in the UK, national vaccine recommendations, including specific vaccination of hyposplenic patients, are published and regularly updated in the 'Green Book' on 'Immunisation against Infectious Disease'.[3]

In the UK, the incidence of PCV13-serotype pneumococcal disease is very low because of the highly successful childhood immunisation programme. The risk of exposure to PCV13 serotypes for high-risk patients, including hyposplenic patients, is, therefore, low. Additionally, nearly all children aged <18 years (born since September 2004) will have received PCV7 or PCV13 as part of the UK national childhood immunisation programme. Consequently, PPV23, which protects against 11 additional serotypes compared with PCV13, is the mainstay of individual protection against pneumococcal disease in high-risk individuals, including hyposplenic patients, and adults aged ≥65 years.

In a newly diagnosed hyposplenic patient, it is important to ensure that they have received all their eligible vaccines according to the national immunisation schedule. Guidelines for individuals with uncertain or incomplete immunisation status in the UK are published and regularly updated online.[67]

Since the current vaccines do not protect against all pneumococcal, *H. influenzae* and meningococcal strains, emphasis must be placed on daily antibiotic prophylaxis in addition to the recommended vaccines for high-risk hyposplenic patients.

1. Infants with hyposplenism diagnosed before 2 years of age should be immunised according to the national immunisation schedule (**Grade 1A**), followed by PPV23 on their second birthday (**Grade 1B**). PPV23 is delayed until 2 years of age because younger children respond poorly to polysaccharide vaccines.[68] **Those with incomplete or uncertain immunisation should receive their eligible vaccinations according to the UKHSA guidelines,[67] including PCV, before receiving their PPV23 dose from 2 years of age and at least 8 weeks after their last PCV dose.**
2. Children aged ≥2 years and adults should receive one PPV23 dose, irrespective of their prior PCV vaccination status (ensuring that this dose is at least 2 months after their last PCV dose) (**Grade 1B**).
3. PPV23 boosters for hyposplenic patients are recommended every 5 years for life because of waning protection (**Grade 1B**) (this may change if higher-valent PCVs (PCV20 and above) replace PPV23 in the national immunisation programme) (Grade 1B). There is no need to test for pneumococcal antibodies before or after boosting.

PCV20 is licensed for adults but, as of May 2023, is not part of the UK immunisation programme—PCV20 may be used as an alternative to PPV23 in hyposplenic adults, but there is currently no evidence to support the need for or timing of boosters with PCV20.

Although serotype-specific pneumococcal antibody testing is available for most vaccine serotypes, interpretation of the results for recommending additional pneumococcal vaccination is difficult because of the large number of

TABLE 2 Infants and children up to 10 years of age.

	<1 year	1 year	2 years	3–10 years
Hib	Routine Hib-containing vaccine at 8, 12 and 16 weeks	Routine Hib/MenC on first birthday	No further Hib doses needed	
Pneumococcal	Routine PCV at 12 weeks	Routine PCV on first birthday	PPV23 on second birthday **/***	Repeat PPV23 every 5 years (no need to check pneumococcal antibody levels) ***
Meningococcal	Routine 4CMenB vaccine at 8 and 16 weeks of age	Routine Hib/MenC and 4CMenB on first birthday		
	MenACWY *	Additional MenACWY at 1 year, irrespective of number of MenACWY doses received before first birthday. To be given at least 4 weeks after Hib/MenC	If MenACWY not given on or after first birthday, give one dose of MenACWY ** If asplenia diagnosed in someone who has never received MenB vaccination, give two doses of 4CMenB at least 4 weeks apart ****	If MenACWY not given on or after first birthday, give one dose of MenACWY ** If asplenia diagnosed in someone who has never received MenB vaccination, give two doses of 4CMenB at least 4 weeks apart ****
Annual influenza vaccine	Annual influenza vaccine (from 6 months of age)	Annual influenza vaccine		
COVID-19 vaccine	COVID-19 vaccine	COVID-19 vaccine according to national recommendations		
Travel to meningitis-endemic areas				
MenACWY conjugate vaccine ideally at least 2 weeks prior to travel unless received the vaccine in previous 12 months				

Note: If a child is identified to have incomplete or uncertain immunisations according to the UK national immunisation programme, then refer to the UKHSA Document and update any missing vaccinations before administering any additional vaccinations for asplenics. Colour of text: Blue = routine immunisations; Red = additional vaccines for hyposplenics; Black = no action needed.

*Two doses of MenACWY conjugate vaccine at least 8 weeks apart if aged <6 months (these doses can be given at the same visit at the routine 4CMenB doses), or one dose of MenACWY conjugate vaccine if aged between 6 months and 1 year. ** Or as soon as asplenia is diagnosed after second birthday. *** PCV20 may be used as an alternative to PPV23 in hyposplenic adults, but there is currently no evidence to support the need for or timing of boosters with PCV20. **** MenB-fHbp (Trumenba®) may be used as an alternative for individuals aged 10 years and older as a two-dose (6-month interval) or a three-dose regimen (two doses at least 1 month apart, with third dose at least 4 months after second dose).

vaccine serotypes involved. Additionally, the World Health Organization (WHO) has recommended a serotype-specific protective IgG threshold of ≥0.35 μg/mL, but individual serotypes are known to have different antibody thresholds for protection.[69] Importantly, too, the relevance of this threshold for adults, especially older people, is unclear.[70] Therefore, routine testing for serotype-specific or total pneumococcal antibody levels to decide on the timing or need for pneumococcal boosters is not recommended.

Timing of vaccination

In patients undergoing splenectomy, PPV23 should be given at least 2 weeks before the procedure to those who are eligible. In one study, postvaccination total pneumococcal antibody levels following splenectomy did not differ significantly from vaccinated control adults, whether vaccination was undertaken immediately or delayed for 14 days after splenectomy; functional antibody responses were, however, better with delayed vaccination (14 days postsplenectomy).[71] There are no data on the timing of PCV vaccination in young children who require elective or undergo emergency splenectomy, but it would be appropriate to use similar timings for the first PCV dose in this rare situation. Care should be taken to ensure patients are not lost to follow-up where the first vaccination is planned after discharge from the hospital.

All other at-risk unimmunised patients should be immunised at the first opportunity. Where possible, immunisation should be undertaken at least 2 weeks before immunosuppressive therapy, delayed at least 3 months after immunosuppressive therapy or radiotherapy or until recovery of adequate immunological function where this can be appropriately assessed.[72]

Hib vaccination

Haemophilus influenzae can be characterised as one of six different serotypes (a–f) or as non-typeable (also known as non-encapsulated) strains. Hib is the most virulent and, prior to routine immunisation, accounted for over 80% of all invasive *H. influenzae* infections, mainly in children

TABLE 3 Children older than 10 years and adults.

2 weeks before or 2 weeks after splenectomy or when hyposplenia diagnosed		Long term
Hib	No longer recommended	
Pneumococcal	One dose of PPV23 */**	Repeat PPV23 every 5 years (without checking pneumococcal antibody levels) **
Meningococcal	One dose of MenACWY */*** *If never received MenB vaccination give two 4CMenB doses* at least 4 weeks apart* */***	Annual influenza vaccine and COVID-19 vaccine according to national recommendations
Travel to meningitis-endemic areas		
MenACWY conjugate vaccine ideally at least 2 weeks prior to travel unless received the vaccine in previous 12 months		

Note: Colour of text: Red = additional vaccines for hyposplenics; Black = no action needed.

*Can be given at same visit as other vaccinations. ** PCV20 may be used as an alternative to PPV23 in hyposplenic adults, but there is currently no evidence to support the need for or timing of boosters with PCV20. *** MenB-fHbp (Trumenba®) may be used as an alternative for individuals aged 10 years and older as a two-dose (6-month interval) or a three-dose (two doses at least 1 month apart, with third dose at least 4 months after second dose).

<5 years of age. The Hib conjugate vaccine was introduced into the UK childhood immunisation programme in 1992 and resulted in a rapid and sustained reduction in the incidence of invasive Hib disease across all age groups through a combination of direct (vaccinated individuals) and indirect (population) protection; in the UK, annual Hib disease incidence remains below one case per million population, with only 67 Hib cases among 3523 laboratory-confirmed invasive *H. influenzae* infections during 2012–2016.[73] Hyposplenic individuals are at increased risk of Hib disease, although the risk is not as high as for pneumococcal disease.

The current UK immunisation schedule offers three doses of a Hib-containing combination vaccine at 8, 12 and 16 weeks of age, followed by a booster dose at 1 year, which is given as a Hib/Meningococcal group C (MenC) combination conjugate vaccine (Menitorix®; GSK Biologicals, UK). There are currently no monovalent Hib conjugate vaccines available in the UK, and the Hib/MenC vaccine offered to infants on their first birthday will soon be discontinued and replaced with a multivalent (6-in-1) Hib-containing vaccine at 12 or 18 months of age.[74]

Change of practice: Since Hib disease is rare because of the successful national UK immunisation programme and because of the lack of availability of a monovalent Hib conjugate vaccine, *additional* vaccination against Hib is no longer recommended for patients with hyposplenism (Grade 1B). Note that this recommendation may not apply outside the UK.

Note that the Hib conjugate vaccine does not protect against other encapsulated *H. influenzae* serotypes, for which there are no licensed vaccines, again highlighting the importance of daily antibiotic prophylaxis for protection against infection in high-risk hyposplenic patients.

Meningococcal vaccination

Meningococcal disease continues to cause significant morbidity and mortality across all age groups. Hyposplenic patients are at particularly high risk of meningococcal disease. Twelve meningococcal serogroups are recognised, of which four (serogroups B, C, W and Y) are responsible for most cases of invasive meningococcal diseases in the UK and across Europe.[75] Serogroup A disease is rare in Europe but caused large epidemics across the African Meningitis Belt prior to mass vaccination with the MenA conjugate vaccine.[76] Serogroups C, W and Y are well-controlled in the UK because of a highly effective adolescent meningococcal ACWY conjugate vaccine programme, which not only provides teenagers and young adults direct protection against meningococcal disease but, since adolescents are the main nasopharyngeal carriers of meningococci and because conjugate vaccines prevent carriage acquisition, also interrupts transmission, thus providing indirect protection across the population.[77] In addition to the adolescent MenACWY conjugate vaccine programme in the UK, a Hib/MenC conjugate vaccine is also offered to infants on their first birthday—this vaccine will soon be discontinued and replaced with a multivalent (6-in-1) Hib-containing vaccine at 12 or 18 months of age.[74] Because of the successes of the current national immunisation programme, cases of meningococcal A, C, W and Y disease are rare across all age groups in the UK.

Additionally, the current UK childhood immunisation programme includes two doses of a four-component, recombinant-protein-based vaccine (4CMenB, Bexsero®; GSK Biologicals) against MenB disease, given at 8 and 16 weeks of age, followed by a booster at 1 year.[78] The vaccine protects against most but not all MenB strains causing invasive disease because some MenB strains many not possess cross-reactive vaccine antigens on their cell surface.[79] On the other hand, the vaccine may protect against other meningococcal serogroups[80] and potentially against the related *N. gonorrhoea*[81] that possess cross-reactive vaccine antigens. 4CMenB, however, has no effect on meningococcal carriage and, therefore, does not provide any indirect (population) protection.[82]

Another protein-based MenB vaccine composed of two recombinant lipidated meningococcal factor H binding protein (fHbp) variant proteins (MenB-fHbp, Trumenba®; Pfizer Ltd.) is also licensed for individuals aged 10 years and older as a two-dose (6-month interval) or a three-dose (two doses

at least 1 month apart, with the third dose at least 4 months after the second dose) schedule.[83] MenB-fHbp is not part of the UK immunisation programme but could be used as an alternative to 4CMenB in hyposplenic children aged ≥11 years and adults. The two vaccines are not interchangeable.

Based on experience with the MenC and other conjugate vaccines, the immunity provided by the MenACWY conjugate vaccine is expected to be higher and longer lasting and to confer less risk of immunological tolerance than the MenACWY plain polysaccharide vaccine. For this reason, the MenACWY conjugate vaccine is recommended in preference to the plain polysaccharide meningococcal vaccine for all age groups.[84]

1. Infants diagnosed with hyposplenism in the first year of life should receive the MenACWY conjugate vaccine (two doses at least 8 weeks apart if aged <6 months [these doses can be given at the same visit at the routine 4CMenB doses], or one dose if between 6 and 12 months of age) **(Grade 1B)**. They will have the routine Hib/MenC vaccine dose at 1 year as part of the childhood immunisation schedule (given at least 4 weeks after the last MenACWY conjugate dose) and should then receive an additional MenACWY conjugate vaccine booster at 1 year (at least 4 weeks after the routine Hib/MenC dose) **(Grade 1B)**.
2. All children aged ≥1 year and adults should receive one dose of the MenACWY conjugate vaccine, irrespective of their previous meningococcal vaccination status **(Grade 1B)**. For children who have received the previous MenACWY conjugate vaccine, this dose serves as a booster—if hyposplenism is diagnosed on or after their second birthday, this dose can be given at the same visit as PPV23 **(Grade 1B)**.
3. If asplenia is diagnosed in someone who has never received any MenB vaccination, follow the UKHSA Guidelines for unimmunised children if aged less than 2 years. For unimmunised older children—from their second birthday onwards, and for unimmunised adults, give two doses of 4CMenB at least 4 weeks apart. **(Grade 1B)**.

Travel to high-risk countries—See the National Travel Health Network and Centre (NaTHNaC.net)

All hyposplenic individuals intending to travel to a country where there is an increased risk of meningococcal serogroup A, C, W or Y disease should receive the MenACWY conjugate vaccine ideally at least 2 weeks before travelling (but can be given at any time before travel) if they have not had the vaccine in the previous 12 months. **(Grade 1C)**.

Influenza, COVID-19 and respiratory syncytial virus vaccination

Given the risk of secondary bacterial infection, the annual influenza vaccine continues to be recommended for hyposplenic patients. **(Grade 1A)**.[3,85] They should be immunised with an inactivated vaccine; current UK advice is for a quadrivalent vaccine following World Health Organization guidance. The households of people who are immunosuppressed are also recommended to be vaccinated against influenza **(Grade 1B)**; children up to 18 years of age should be immunised according to the national immunisation schedule **(Grade 1B)**, with those aged 6 months to less than 2 years offered a suitable quadrivalent inactivated influenza vaccine and older children offered the live attenuated influenza vaccine unless medically contraindicated **(Grade 1B)**. Children under 9 years of age who have not previously been vaccinated against influenza should be offered two doses of the live attenuated influenza vaccine given at least 4 weeks apart **(Grade 1B)**.[85]

Patients should also receive the COVID-19 vaccination according to national recommendations for high-risk individuals, including hyposplenics, from 6 months of age (Grade 1B).[3] As with influenza, similar recommendations are made for the vaccination of household contacts to reduce the risk of COVID-19 in hyposplenic patients **(Grade 1C)**. The UK currently recommends all those aged 16 years and above be offered COVID-19 seasonal vaccination if they are in the same household or a carer of a person who is immunosuppressed **(Grade 1C)**.[86]

A *long-acting* vaccine for respiratory syncytial virus (RSV) has been licensed recently for adults but is not currently part of the UK national immunisation programme.

VACCINE RECOMMENDATIONS

- **Vaccines should ideally be administered 2 weeks before or 2 weeks after splenectomy (Grade 1B), but they can be given at any time before or after splenectomy (Grade 2B).**
- **Vaccines should ordinarily be administered as soon as practicable after recognition of non-surgical hyposplenism (Grade 1B), but specific scheduling may be required in the context of recovery from immunosuppression (Grade 1C).**
- **Since the current vaccines do not protect against all pneumococcal, *H. influenzae* and meningococcal strains, emphasis must be placed on daily antibiotic prophylaxis in addition to the recommended vaccines in high-risk hyposplenic patients (Grade 1B).**

This is a rapidly evolving field, and reference should always be made to the latest Green Book[3] or equivalent advice.

Pneumococcal vaccination

- **Hyposplenic infants should be immunised according to the national immunisation schedule with PCV13 at 8 weeks and 1 year of age (Grade 1A). This should be followed by PPV23 on their second birthday (Grade 1B).**

- **Children aged ≥2 years and adults at diagnosis of hyposplenism should receive PPV23 irrespective of their prior PCV vaccination status and at least 2 months after their last PCV dose (Grade 1B).**
- **PPV boosters should be offered every 5 years (Grade 1B).**
- **There is no role for measuring total or serotype-specific pneumococcal antibody responses to guide the decision or timing of PPV boosters (Grade 1B).**
- **PCV20 is licensed for adults but, as of May 2023, is not part of the UK immunisation programme—PCV20 may be used as an alternative to PPV23 in hyposplenic adults, but there is currently no evidence to support the need for or timing of boosters with PCV20 (Grade 2D).**

H. influenzae serotype b (Hib) vaccination

- **Hyposplenic infants should be immunised according to the national immunisation schedule with a Hib-containing vaccine at 8, 12 and 16 weeks of age (Grade 1A).**
- **The Hib/MenC conjugate vaccine should be given at 1 year of age. Note that this vaccine will soon be discontinued in the UK and replaced with another multivalent (6-in-1) Hib-containing conjugate vaccine in the second year of life.**
- **Given the excellent population control and lack of a monovalent Hib-containing conjugate vaccine, additional vaccination against Hib is no longer recommended for patients with hyposplenism (Grade 1B).**

Meningococcal vaccination

MenACWY vaccination

- **Infants diagnosed with hyposplenism in the first year of life should receive the MenACWY conjugate vaccine (two doses at least 8 weeks apart if aged <6 months [these doses can be given at the same visit at the routine 4CMenB doses], or one dose if between 6 and 12 months of age) (Grade 1B). They will have the routine Hib/MenC vaccine dose at 1 year as part of the childhood immunisation schedule (given at least 4 weeks after the last MenACWY conjugate dose) and should then receive an additional MenACWY conjugate vaccine booster at 1 year (at least 4 weeks after the Hib/MenC dose) (Grade 1B).**
- **All children aged ≥1 year and adults should receive one dose of the MenACWY conjugate vaccine, irrespective of their previous meningococcal vaccination status (Grade 1B). For children who have received previous MenACWY, this dose serves as a booster. If hyposplenism is diagnosed on or after their second birthday, this dose can be given at the same visit as PPV23 (Grade 1C). Children who have received a MenACWY conjugate vaccine (as part of the routine adolescent MenACWY immunisation programme) do not need an additional dose (Grade 1C).**
- **The quadrivalent MenACWY conjugate vaccine is recommended in preference to the plain polysaccharide meningococcal ACWY vaccine for all age groups (Grade 1A).**
- **There is currently no evidence to recommend booster doses of the MenACWY conjugate vaccine (Grade 1C).**

Travellers to endemic areas should receive the quadrivalent MenACWY conjugate vaccine before travelling if they have not received a dose in the previous 12 months (Grade 1C). The current recommendation for hajj/umrah pilgrimages to Saudi Arabia can be found here: NaTHNaC website: https://travelhealthpro.org.uk/factsheet/19/hajj-and-umrah.

MenB vaccination

- **Hyposplenic infants should be vaccinated with MenB according to the national immunisation schedule at 8 and 16 weeks, together with a further dose at 1 year (Grade 1A).**
- **If asplenia is diagnosed in someone who has never received MenB vaccination, follow the UKHSA Guidelines for unimmunised children if aged less than 2 years. For unimmunised older children (from their second birthday onwards) and for unimmunised adults, give two doses of 4CMenB at least 4 weeks apart (Grade 1B).**
- **4CMenB is currently part of the UK national immunisation programme, but MenB-fHbp (Trumenba®, Pfizer Ltd) may be used as an alternative for individuals aged 10 years and older, albeit at a different schedule either two doses (at a 6-month interval) or three doses (2 doses at least 1 month apart, with the third dose at least 4 months after the second dose) (Grade 2C). There is currently no evidence to recommend booster MenB vaccine doses (Grade 2D).**

Influenza and COVID-19 vaccination

All patients should receive a yearly influenza vaccination from 6 months of age (Grade 1A). Patients should also receive the COVID-19 vaccination according to national recommendations (Grade 1B).

ANTIBIOTIC PROPHYLAXIS

The increased risk of infection in patients with an absent or non-functioning spleen is lifelong but is highest early after splenectomy. As discussed above, most instances of serious infection are due to encapsulated bacteria, with pneumococcal disease being predominant. The impact of IPD and its

high mortality have had a major influence on both vaccination and antibiotic strategies. Other more unusual infections are well described.

Penicillin prophylaxis is highly effective at preventing pneumococcal infection in children with sickle cell disease and this experience provides the main evidence for continuing prophylaxis in other at-risk groups.[87–89] Failures of both vaccination and antibiotic prophylaxis are well documented.

The risk of sepsis postsplenectomy is highest immediately postoperatively and over the next few years. After splenectomy for trauma, the risk is greatest in the immediate postoperative period (during hospitalisation), and antibiotic prophylaxis should include this period.[90] However, while the risk gradually declines, cases of fulminant infection have been reported more than 20 years after splenectomy. The American Guidelines suggest prophylaxis should be continued for at least the initial 1 or 2 years after splenectomy to cover the initial period of greatest risk.[55] Spleen Australia recommends prophylaxis for a minimum of 3 years postsplenectomy.[47] These recommendations are based on expert opinion rather than robust data.

The risk is greater in children up to the age of 16 years and in adults over 50 years (reviewed by William et al.[6]). Additional risk factors include surgery for haematological malignancy as opposed to trauma, ongoing immunosuppression, poor or no response to pneumococcal vaccination and previous IPD.[91–93] It is not certain how these individual risk factors are linked; however, some patients are at much greater risk than others, and this information may be used in risk stratification.

The use of lifelong prophylactic antibiotics directed against pneumococcal disease for all patients has been BSH policy for more than 20 years.[1] The use of lifelong penicillin prophylaxis beyond the first 1–3 years postsplenectomy, however, has potential disadvantages as it can be associated with the development of bacterial resistance, may have side effects including allergy and may be associated with poor adherence.[94] Hence, lifelong antibiotic prophylaxis beyond the first 1–3 years postsplenectomy may be best reserved for patients who remain at high risk of pneumococcal infection. The previous BSH Guideline supported the continued use of penicillin prophylaxis (or equivalent) in hyposplenic patients up to the age of 16 years and in those over 50 years of age. More recent guidance suggests that prophylaxis be given at least for all asplenic children until the age of 5 years, ensuring at least two complete years of prophylaxis.[47,55] This was based on the PROPS II study, in which children with sickle cell disease who had received penicillin prophylaxis for at least 2 years were randomised to continue penicillin prophylaxis or not after 5 years of age. However, children with a previous splenectomy were excluded from this study, and it was underpowered.[55,89]

Given the lack of robust data, it would be reasonable to use penicillin prophylaxis for patients up to the age of 5 years and for those over 65 years of age.

The following high-risk groups need careful counselling and follow-up to ensure adherence to antibiotic prophylaxis (Box 1).

BOX 1 Patients at high-risk of overwhelming sepsis who need careful counselling and follow-up to ensure adherence to antibiotic prophylaxis.

- Patients who have had a previous episode of invasive pneumococcal disease.
- Patients treated for haematological malignancy, particularly those who have received splenic irradiation or who have ongoing graft-versus-host disease or ongoing immunosuppression.
- Patients at the extremes of age.
- Patients in the immediate postsplenectomy period and for 1–3 years postsplenectomy.

The published standards of care for sickle cell disease recommend penicillin prophylaxis beyond 5 years of age with the option of continuing it in adulthood or keeping an emergency supply on standby at the treatment dose.[95]

These factors enable some risk stratification, and those with lowest risk may choose to stop regular antibiotic prophylaxis. Some will choose to continue, and those with higher risk should be encouraged to continue indefinitely.[96,97]

At the first indication of systemic infection (especially high fever), all patients should have access to and should start immediate treatment with appropriate antibiotics, based on specific locally agreed protocols. In patients on regular antibiotic prophylaxis, treatment should include a different antibiotic class. Antibiotic choice should be made according to local microbiological advice and protocols.

Oral penicillins remain the prophylactic antibiotics of choice in areas with low pneumococcal resistance. Specialist microbiological advice should be sought where this is not the case or for travel abroad. In patients with confirmed penicillin allergy, an appropriate macrolide may be substituted, depending on local practice.

Recommendations

- **Prophylactic antibiotics should be used in all patients following splenectomy, in the immediate postoperative period and for 1–3 years thereafter.**
- **Prophylaxis should be given to all asplenic children until the age of 5 years, ensuring at least two complete years of prophylaxis.**
- **Lifelong prophylactic antibiotics should be offered to patients considered at continued high risk of pneumococcal infection (Grade 1B). Factors associated with a high risk of IPD in hyposplenism include extremes of age (less than 5 years and over 65 years of age), a history of previous IPD and splenectomy for underlying haematological malignancy, particularly in the context of ongoing immunosuppression (Grade 1B).**

- **Patients not at high risk after the first 1–3 years should be counselled regarding the risks and benefits of lifelong antibiotics and may choose to continue or discontinue prophylaxis (Grade 2C).**
- **All patients should carry a supply of appropriate antibiotics for emergency use (Grade 1A).**
- **Patients developing symptoms and/or signs of infection, despite the above measures, must be given parenteral antibiotics and admitted urgently to the hospital (Grade 1A).**

RESEARCH AND AUDIT

Regular audit should continue. Readily auditable areas include vaccination rates, adherence to antibiotic prophylaxis and the current outcome of severe infection in asplenic and hyposplenic patients.[97,98] There is a strong case for setting up a national splenectomy registry, starting with a few large centres. There is a lack of sufficient high-quality data to guide antibiotic prophylaxis duration where this is not required lifelong, and this remains an area for further study.

CONCLUSIONS

Infection in patients with an absent or hypofunctional spleen remains largely preventable. Preventative strategies continue to be based on the education of staff and patients, appropriate immunisation schedules and chemoprophylaxis.

AUTHOR CONTRIBUTIONS

Shamez N. Ladhani wrote the sections on immunisation with Ray Borrow. Mamta Garg wrote the section on the causes and diagnosis of hyposplenism. Paula H. B. Bolton-Maggs wrote the section on education and information. Savio Fernandes wrote the section on anti-infection prophylaxis. Simon de Lusignan reviewed the full paper and contributed advice on primary care. All authors contributed to editing and reviewing the manuscript.

ACKNOWLEDGEMENTS

The authors wish to thank Ben Stevenson (Niche Science & Technology Ltd) for his help in undertaking the initial literature review. The BSH General Haematology task force members at the time of writing this guideline were Barbara de la Salle; Charlotte Bradbury; Jayne Parkes; Jennifer Tam; John Brewin; Mohammed Altohami; Nicola Ransome; Noemi Roy; Sara Stuart-Smith; Savio Fernandes; Suzanne Docherty; and Mamta Garg. The authors would like to thank them, the BSH sounding board, and the BSH guidelines committee for their support in preparing this guideline.

CONFLICT OF INTEREST STATEMENT

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a declaration of interests to the BSH and Task Force Chairs, which may be viewed on request. RB performs contract research on behalf of UKHSA for GSK, Pfizer and Sanofi. SdeL has received funding through his University for vaccine-related research from AstraZeneca, GSK, Moderna, Sanofi and Seqirus. He has also been members of advisory boards for AstraZeneca, GSK, Sanofi and Seqirus, with any funding paid to his institution. The other members of the writing group have no conflicts of interest to declare.

REVIEW PROCESS

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every 3 years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made, an addendum will be published on the BSH guidelines website (www.b-s-h.org.uk/guidelines).

DISCLAIMER

While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the BSH, nor the publishers accept any legal responsibility for the content of this guidance.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ladhani SN, Fernandes S, Garg M, Borrow R, de Lusignan S, Bolton-Maggs PHB. Prevention and treatment of infection in patients with absent or hypofunctional spleen: A British Society for Haematology guideline. Br J Haematol. 2024;00:1–15. https://doi.org/10.1111/bjh.19361