

REVIEW

Spleen Australia guidelines for the prevention of sepsis in patients with asplenia and hyposplenism in Australia and New Zealand

Kudzai Kanhutu,^{1,2} Penelope Jones,³ Allen C. Cheng,^{3,4,5} Louise Grannell,^{3,6} Emma Best⁷ and Denis Spelman^{3,8}¹Victorian Infectious Diseases Service, Royal Melbourne Hospital, ²Dentistry and Health Sciences, Faculty of Medicine, The University of Melbourne,³Spleen Australia, Department of Infectious Diseases, ⁴Infection Prevention and Healthcare Epidemiology Unit, ⁶Pharmacy Department, and⁸Microbiology Unit, Department of Pathology, Alfred Health, and ⁵School of Public Health and Preventive Medicine, Monash University, Melbourne,Victoria, Australia, and ⁷University of Auckland and Starship Children's Hospital, Auckland, New Zealand**Key words**

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Correspondence

Kudzai Kanhutu, Peter Doherty Institute, Victorian Infectious Diseases Service, Level 5/792 Elizabeth Street, Melbourne, Vic. 3000, Australia.

Email: kudzai.kanhutu@mh.org.au

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Introduction

Fulminant sepsis is a significant risk in patients following splenectomy, or in patients who have hyposplenism for other reasons, such as congenital asplenia, coeliac disease or following bone marrow transplantation. The incidence of such infections can be reduced by preventive measures, although compliance with recommendations in the literature is poor.^{1,2} The Spleen Australia advisory group, which includes medical, nursing and pharmacy expertise, meets monthly and considers clinical questions received from patients and doctors, as well as recent developments in prevention measures for patients with asplenia/hyposplenism. Previous guidelines³ published in 2008 have been updated, with a draft circulated to previous authors and selected adult and paediatric infectious diseases physicians in both Australia and New Zealand with an interest in immunisation in patients with asplenia/hyposplenism (Table 1). These present guidelines have been endorsed by the Australasian Society for Infectious Diseases. This update was necessary in view of the development of new vaccines, as

Abstract

People with asplenia/hyposplenism are at increased risk of fulminant sepsis, which carries a high mortality rate. A range of preventive measures is recommended although there is ongoing evidence that knowledge of and adherence to these strategies is poor. There have been significant changes in recommended vaccinations since the previously published recommendations in 2008. We provide current recommendations to help Australian and New Zealand clinicians in the prevention of sepsis in patients with asplenia and hyposplenism. The guideline includes Australian epidemiological data, preferred diagnostic techniques and recommendations for optimal antimicrobial prophylaxis and vaccination protocols.

well as new observational data and recommendations from UK,⁴ Canada,⁵ Australia,^{6,7} the United States^{8–10} and New Zealand.^{11,12} In addition to a literature review, several clinicians from New Zealand and Australia were consulted regarding their current practices in relation to patients with asplenia/hyposplenism.

Identifying patients at risk

The number of persons with asplenia/hyposplenism in Australia is unknown. Based on administrative data, Dendle and colleagues documented 2574 surgical splenectomies over 8 years in the state of Victoria, an estimated incidence rate of 6.4 per 100 000 per year.¹³ This would suggest there are around 0.1–0.3%, or 20 000–60 000 Australians with asplenia. However, the incidence of splenectomy may be decreasing with the increasing use of splenic artery embolisation (SAE) following trauma.^{14,15}

Surgical splenectomy, either following trauma or therapeutically, is the most common reason for asplenia.¹³ As such, maximal efforts should be made to preserve healthy splenic tissue and therefore splenic function. Salvage techniques that have been suggested include SAE,

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Table 1 What's new

Patient clinical service for people without a functioning spleen, now operational in Queensland, Tasmania and Victoria
Antibiotic prophylaxis now recommended for adults for at least 3 years after splenectomy
Amoxicillin/clavulanic acid replaces cefuroxime as stand-by antibiotic of choice in children
13 valent pneumococcal conjugate vaccine (Prevenar 13) supersedes the 7 valent (Prevenar 7) and 10 valent PCV (Synflorix).
Introduction of quadrivalent (A, C, W ₁₃₅ , Y) meningococcal conjugate vaccines
Introduction of meningococcal B vaccine in Australia
Link to specific paediatric recommendations and other important resources (via Spleen Australia website)

splenic repair and the embedding of splenic tissue in the omentum.

Medical causes of asplenia/hyposplenism include allogeneic bone marrow transplantation, especially in the presence of chronic graft-versus-host disease, coeliac disease, patients with haemoglobinopathies, systemic lupus erythematosus and inflammatory bowel disease. There is also a small number of patients with familial/congenital asplenia. Patients at risk of hyposplenism, for example, may be monitored for the appearance of Howell-Jolly bodies (HJB).

The presence of intraerythrocytic inclusions called HJB on a blood film is the most commonly used diagnostic marker of asplenia/hyposplenism, although this is an indicator of the spleen's ability to remove damaged cells rather than of immunological function. Quantification of IgM memory B cells may be of use for predicting an individual's capacity to mount an immune response to encapsulated bacteria following splenectomy. A large study found minimal evidence of hyposplenism following embolisation.^{16,17} Another study on patients with portal hypertension/cirrhosis who underwent SAE also had a significant number of patients not found to be hyposplenic.¹⁸

Ultrasound and computerised tomography can be used to identify the presence of the spleen or splenic tissue, but the size of the residual tissue does not reliably correlate with function.¹⁹ However, clinical follow-up is required for a blood film taken 4 or more weeks after procedure to assess presence of HJB. Primary vaccinations may be considered for patients after splenic irradiation, partial splenectomy or SAE.

Incidence of sepsis in patients with asplenia/hyposplenism

The reported incidence varies with the patient group, duration of follow-up, definitions used and the method of estimation. The percentage of patients who develop sepsis post-splenectomy ranges from 3.2% overall,²⁰ 4.4% in children <16 years to higher in those aged <5 years (10.4%); it was 0.9% in adults.²¹ In a long-term follow-up of 8149 American veterans who had undergone splenectomy, the infection risk was still significantly increased more than 10 years after

splenectomy.²² In a recent 2016 study, which included 52 patients with overwhelming post-splenectomy infection (OPSI), these episodes occurred at a median of 6 years after splenectomy.²³

Indications for splenectomy may also play a part in decision-making for appropriate post-splenectomy management. The incidence of infection and mortality post-splenectomy was highest among patients with underlying thalassaemia major, haematological malignancies and sickle-cell anaemia compared with those having post-traumatic splenectomy.²⁰

Minor infections appear to be common.²⁴ Although infections not requiring hospitalisation are unlikely to be associated with significant morbidity and mortality, this finding illustrates the importance of appropriate patient and prescriber education.

Management recommendations

Patients should receive information about the risk of sepsis and strategies to minimise risk

It is paramount that patients with asplenia/hyposplenism and their families know about their increased lifelong risk of bacterial infections and the recommended prevention strategies (Table 2). The most common causative organisms implicated in fulminant sepsis remain the encapsulated bacteria, especially *Streptococcus pneumoniae* and *Neisseria meningitidis*. Infection with *Haemophilus influenzae* type b (Hib) is now less common since the advent of routine vaccination. Families should be educated about recognising early symptoms of a bacterial infection; have and know when to take their emergency supply of antibiotics; and the importance of seeking prompt medical review when unwell.

El-Alfy and El-Sayed²⁵ demonstrated that those patients with asplenia/hyposplenism who have the best knowledge concerning sepsis had the lowest incidence of this outcome. Clinical registries are a potential cost-effective means of preventing OPSI.²⁴ Patients who live in the Australian states of Queensland, Tasmania or Victoria can register (funded by Departments of Health in these states) with Spleen Australia²⁶ and receive an

Table 2 Summary of recommendations for patients with asplenia and hyposplenism

Patients should receive information about the risk of sepsis and strategies to minimise risk.
Patients should be vaccinated against pneumococcal, meningococcal, <i>Haemophilus influenzae</i> type b and influenza infections.
Patients should receive antibiotic prophylaxis.
Patients should have an emergency supply of antibiotics and an appropriate action plan in case of illness.
Patients who travel overseas should receive specialist advice.
Patients who are bitten or scratched by animals should seek medical advice and may well require antibiotics.
Systems should exist to improve adherence to preventative measures.

education kit and reminders. The Spleen Australia website also includes printable vaccination guides for health practitioners and patients, which can be accessed at no cost. In addition, a smartphone application, linked to the Spleen Australia database, exists to assist with health record maintenance and includes key education points for registered patients.

Patients should receive antibiotic prophylaxis

Please refer to Table 3 for current antibiotic prophylaxis recommendations. The optimal duration of antibiotic prophylaxis is controversial. The most conservative existing guidelines⁴ recommend lifelong antibiotics and there is good evidence that the increased risk of sepsis is also lifelong. A recent US paper suggests that 12 months may be adequate particularly in populations with herd immunity for vaccine preventable diseases.¹⁰ Nevertheless recommendations might need to be refined if an individual patient expresses difficulties or uncertainties about taking prophylactic antibiotics for long term. As a minimum we would recommend antibiotic prophylaxis for adults for at least 3 years after splenectomy and for all children with asplenia/hyposplenism up to the age of 5.

Lifelong prophylaxis should be considered in patients with asplenia/hyposplenism who are immunosuppressed, have had an episode of severe sepsis or have undergone splenectomy for a haematological disorder or malignancy, especially if they require ongoing immunosuppression.⁷ Lifelong prophylaxis is also reasonable in hyposplenic patients with additional conditions that may impair their immune response to standard vaccination (e.g. HIV infection). The role of age-related immune senescence may also factor into decisions about lifelong prophylaxis. In all cases, patient education should rigorously reinforce the necessity of early presentation to medical care when unwell, in order to administer emergency antibiotics and maintain vaccination status.

A recent Cochrane review affirms the role of penicillin in reducing the risk of pneumococcal infection in children.²⁸ This Cochrane review identified several unknowns, including the potential impact of the emergence of drug-resistant *S. pneumoniae* on the

effectiveness of antimicrobial prophylaxis and the ideal age for safely withdrawing penicillin. Failures of antibiotic prophylaxis have been reported; hence, patients should be warned that prophylaxis reduces but does not eliminate the risk of sepsis.

Dental procedures do not require additional antibiotic cover unless the patient has an associated medical condition.⁷ Patients undergoing surgery may be at an increased risk of post-operative infections²⁹ and therefore the usual perioperative antimicrobial prophylaxis should be given.

Patients should have an emergency antibiotic supply

Patients should have an emergency antibiotic supply (Table 3) irrespective of prophylaxis, with instructions to take in the event of any sudden onset of unexplained fever, malaise, chills or other constitutional symptoms. Emergency antibiotics are only a temporising measure and urgent medical attention should always be sought. Patients should be diligent in checking the expiry dates on the packets of their emergency supply of antibiotics.

Patients should be vaccinated against pathogens associated with OPSI

Vaccines against encapsulated organisms are considered to be both safe and generally effective in preventing OPSI. The most common vaccine-preventable infections are invasive pneumococcal and meningococcal sepsis. Patients choosing not to receive the recommended additional vaccines need to be counselled about their risk of not optimising an important infection prevention strategy.

Table 4 summarises the current Spleen Australia vaccination recommendations for adults. For more detailed adult recommendations and the recommended primary vaccinations for patients undergoing embolisation, refer to Spleen Australia website (www.spleen.org.au).

The majority of people with asplenia/hyposplenism on the Spleen Australia registry are adults. Recommendations for children with asplenia and hyposplenism and adult patients who are partially vaccinated can access the

Table 3 Recommended antibiotic prophylaxis and emergency management for patients in Australia with asplenia/hyposplenism^{6,7,26,27}

Indication	Antibiotic and dose	Patients allergic to penicillins†‡
Antibiotic prophylaxis for patients with asplenia and hyposplenism	Adults: Amoxicillin 250 mg daily or phenoxymethylpenicillin 250 mg orally 12 hourly Children§: Amoxicillin 20 mg/kg (up to 250 mg) orally daily or phenoxymethylpenicillin – child younger than 1 year: 62.5 mg; 1–5 years: 125 mg orally 12 hourly	Adults: Roxithromycin 150 mg orally daily or erythromycin 250 mg orally daily/erythromycin ethyl succinate 400 mg orally daily Children§: Erythromycin – child 1 month or older: 10 mg/kg (up to 250 mg) orally daily or erythromycin (ethyl succinate formulation) child 1 month or older: 10 mg/kg (up to 400 mg) orally daily or roxithromycin 4 mg/kg (up to 150 mg) orally daily
Emergency antibiotics	Adults: Amoxicillin 3 g starting dose orally followed by 1 g 8 hourly Children§: Amoxicillin + clavulanic acid 22.5 mg/kg/dose amoxicillin component (max. 875 mg/dose), orally, twice daily (use DUO preparation)	Adults: Roxithromycin 300 mg orally daily or erythromycin 1 g orally 6 hourly Children§: Clarithromycin 7.5 mg/kg/dose (up to 500 mg) orally 12 hourly or roxithromycin 4 mg/kg (up to 150 mg) orally daily

†Patients can be referred to specialist for assessment of penicillin allergy. ‡The choice of antibiotics, especially in patients with a known allergy to penicillin, can depend on the type of allergy, patient tolerance, comorbidities, local *Streptococcus pneumoniae* antibiotic resistance rates, cost and accessibility. Alternative or second-line prophylactic options may include trimethoprim/sulfamethoxazole (co-trimoxazole) or a cephalosporin; an alternative emergency antibiotic includes moxifloxacin in adults. §Guidelines for individuals aged under 18 years can be found on the Spleen Australia website (https://spleen.org.au/VSR/files/RECOMMENDATIONS_Spleen_Registry_p.pdf).

up-to-date vaccine recommendations on the Spleen Australia website (<https://spleen.org.au/VSR/information.html>).

If a patient has a bleeding disorder and there is concern about giving vaccinations, consultation with the person's physician or a haematologist is recommended.

Table 4 Vaccines recommended for adults (>18 years) with asplenia/hyposplenism who have not previously been vaccinated†‡

Organism prevented	Primary vaccinations	Revaccinations
<i>Pneumococcus</i>	Conjugate (Prevenar 13) 0.5 mL IM	8 weeks later Polysaccharide (Pneumovax 23) 0.5 mL IM/SC
<i>Meningococcus</i>	AND Conjugate ACWY (Menveo, Menactra, Nimenrix) 0.5 mL IM	8 weeks later Conjugate ACWY (Menveo, Menactra, Nimenrix) 0.5 mL IM
	Recombinant B (Bexsero) 0.5 mL IM	8 weeks later Recombinant B (Bexsero) 0.5 mL IM
<i>Haemophilus influenzae</i> type b	Conjugate Hib (Liquid PedvaxHIB, Hiberix) 0.5 mL IM	No boosters required
Influenza	Influenza vaccine	Each year (during flu season) Influenza vaccine

†Give initial vaccines 7–14 days prior to elective splenectomy at least 7 days after emergency splenectomy. Verbal consent should be obtained prior to administration of vaccines. ‡Embolised patients receive only the 23 valent pneumococcal polysaccharide vaccine, one quadrivalent meningococcal conjugate vaccine and *Haemophilus influenzae* type b as initial vaccines and if appropriate, influenza vaccine. Refer to Spleen Australia website for embolisation guideline. IM, intramuscular; SC, subcutaneous.

Timing of vaccination

Patients having an elective splenectomy should ideally commence vaccination at least 7–14 days prior to the procedure. The optimal timing for receipt of vaccine following emergency splenectomy remains uncertain. There is evidence that vaccine responses to the 23 valent pneumococcal polysaccharide vaccine (23vPPV) are the same at days 14 and 28 following splenectomy as in healthy adults.³⁰ However, functional antibody responses were significantly higher when 23vPPV was given at day 14 following splenectomy compared with that given at day 7. Responses to newer conjugate vaccines in relation to the timing of splenectomy are not yet known. The uncertainty in the effectiveness of early vaccination may need to be balanced against the risk of loss to follow up following hospital discharge in each individual.

In the setting of planned immunosuppression, chemotherapy or radiotherapy, if possible vaccinations should be undertaken no later than 2 weeks before immunosuppressive therapy or delayed at least 3–6 months after chemotherapy or radiotherapy or until adequate immunological function. Discussion with the patient's specialist physician is recommended.

In adults all recommended vaccines can be given at the same time at different injection sites. The same applies for children with the exception of 13 valent pneumococcal conjugate vaccine (13vPCV) and influenza vaccine, which should be given 3 days apart in those ≤ 4 years old owing to concerns about increased risk of febrile convulsions.²⁷

Although the World Health Organization has set out a serotype-specific IgG level of $\geq 0.35 \mu\text{g/mL}$ ⁴ as indicative of protection for pneumococcal infection in young children receiving the conjugate vaccine, the effectiveness (and cost-effectiveness) of revaccination based on antibody levels has not been established and is not currently recommended. A study of 145 patients with asplenia demonstrated strong serological responses to 7 valent pneumococcal conjugate vaccines (7vPCV). However, post-vaccine pneumococcal sepsis was nonetheless diagnosed in 3.3% of splenectomised survivors, suggesting that vaccination alone cannot be relied upon as a preventive measure.³¹

Pneumococcal vaccination recommendations

The commonly used vaccines in Australia and New Zealand are outlined in Table 5. 13vPCV has superseded both the 7 valent and 10 valent formulations. The 13vPCV is more immunogenic in children, especially in those less than two years old. Compared with the 23vPPV, it provides better T-cell-mediated immune memory, avidity maturation of elicited antibody,

mucosal immunity and herd immunity.³² In children, pneumococcal vaccination should follow the national schedule, with additional doses recommended.^{6,11,12,27}

For adults 13vPCV is given only once and currently no boosters are recommended. Three doses of 23vPPV are recommended in a patient's lifetime: initial dose, the second dose (first revaccination) is recommended at 5 years and a third dose (second revaccination) to be given at 65 years or >50 years in the indigenous population. If asplenia is diagnosed at an age of >65 years (>50 years in the indigenous population), then three doses of 23vPPV should be given 5 years apart. If 23vPPV is due and the patient has not had a 13vPCV previously, then give 13vPCV first and then 8 weeks later administer a 23vPPV.

There are some data to suggest that administering 13vPCV before 23vPPV results in higher antibody titres.¹⁰ It has been proposed that antibodies generated to 23vPPV could potentially bind to 13vPCV antigens impairing the immune response. Therefore, it is advised that if 23vPPV is inadvertently given before a dose of 13vPCV, subsequent dose of 13vPCV must be given >12 months after the dose of 23vPPV.

Meningococcal vaccination recommendations

Currently available vaccines include the conjugate meningococcal C (MenCCV), polysaccharide meningococcal vaccines (4vMenPV), conjugate quadrivalent meningococcal vaccines (4vMenCV) and new multi-component peptide-based meningococcal Group B vaccine (MenBV). MenBV is currently not licenced in New Zealand.

The 4vMenCV and the MenBV vaccines are recommended, two doses of each vaccine 8 weeks apart. 4vMenCV and MenBV can be given at the same time. Booster doses of 4vMenCV vaccine have been recommended every 5 years. No booster doses of MenBV are presently recommended. The quadrivalent meningococcal conjugate vaccines (4vMenCV) have replaced both the meningococcal polysaccharide (4vMenPV) and C conjugate vaccines (MenCCV).

The available 4vMenCV vaccines are licenced only in patients up to 55 years and MenBV vaccine up to 50 years. Despite the lack of studies, Spleen Australia recommends the use of 4vMenCV vaccines for patients >55 years and MenBV for those >50 years due to the increased risk of meningococcal disease.

The dosing strategy, vaccine used and minimum interval for administering meningococcal vaccination in paediatrics are dependent on the patient's age at the time of diagnosis.^{6,11,27}

Due to a reported high incidence of febrile reactions, it is advised that children under the age of 2 receive a

Table 5 Vaccine types and brand names

Pathogen	Vaccine type	Australian trade name	New Zealand trade name
Pneumococcus	13 valent pneumococcal conjugate vaccine (13vPCV)	Prevenar 13	Prevenar 13
	23 valent polysaccharide pneumococcal vaccine (23vPPV)	Pneumovax 23	Pneumovax 23
Meningococcus	Recombinant multi-component meningococcal B vaccine (MenBV)	Bexsero	Not available
	Quadrivalent (A, C, W ₁₃₅ , Y) meningococcal conjugate vaccine (4vMenCV)	Menactra, Menveo, Nimenrix	Menactra (MCV4-D)
	Meningococcal conjugate C vaccine (MenCCV) †	Meningitec, Menjugate, NeisVac-C	NeisVac-C
	Quadrivalent (A, C, W ₁₃₅ , Y) meningococcal polysaccharide vaccine (4vMenPV) †	Mencevax, Menomune	Mencevax

†These classes of vaccine have been superseded.

prophylactic dose of paracetamol within 30 minutes of MenBV administration, and can be followed by two more doses of paracetamol, given 6 h apart. MenBV may be administered at the same time as other vaccinations in the national immunisation schedule, but must be given at a separate injection site. Refer to the Spleen Australia website for complete paediatric meningococcal vaccine guidance.

Haemophilus influenzae type b vaccination

Hib vaccination is recommended for both children and adults. Children under the age of 5 who have received all scheduled vaccine doses do not require a booster dose following splenectomy. The current Australian Immunisation Handbook and Spleen Australia do not require a further vaccine if the primary four-dose course has been administered.⁶ More conservative guidelines in New Zealand recommend that older children and adults should receive a single dose of Hib vaccine at the time of their asplenia diagnosis regardless of their prior Hib vaccine status.^{4,11,12}

Hib vaccine has been demonstrated to be immunogenic in patients following splenectomy, although the immune response was significantly reduced compared with normal controls,³³ and antibody levels declined more rapidly in splenectomised patients.

Influenza vaccination

Inactivated influenza vaccine is recommended annually for patients with asplenia/hyposplenism over 6 months of age and is publicly funded in Australia. It is assumed that prevention of influenza will lessen the risk of secondary bacterial infection, including pneumococcal infection. It is recommended that children under the age of 9 and immunosuppressed adults with asplenia/hyposplenism who have not received an influenza vaccine previously should receive two doses of influenza vaccine 4 weeks apart in their first year of receiving influenza

vaccine. A single annual dose is recommended thereafter.^{6,27}

Patients who travel overseas should receive specialist advice

Patients should be aware of the risk of severe malaria and take optimal precautions to prevent infection by means of antimalarial prophylaxis, mosquito repellents and other barrier precautions. In keeping with current immunisation recommendations, travellers with asplenia/hyposplenism should have 4vMenCV when travelling to high-risk areas (e.g. Sub-Saharan Africa) or carrying out the Hajj pilgrimage, where multiple meningococcal serotypes circulate. Asplenia/hyposplenism in its own right is not a contraindication for any vaccine; however, live vaccines may be contraindicated because of an underlying medical condition.^{6,12} Specialist advice should be sought regarding risks associated with endemic and emerging infectious diseases, such as non-typhoidal salmonella and Zika virus. We recommend that patients seek expert travel advice at least 4 weeks prior to overseas travel.

Patients who are scratched or bitten by animals should receive antibiotics

There is an increased risk of severe sepsis in patients with asplenia/hyposplenism who are scratched or bitten by animals. Dog bites in particular are associated with severe sepsis due to *Capnocytophaga canimorsus*. Such patients should be warned of this risk, informed to apply an antiseptic agent to the puncture site and have adequate antibiotic cover following such bites (e.g. amoxicillin/clavulanic acid for 5 days). Patients allergic to penicillins can use a combination of clindamycin and ciprofloxacin.

Systems should exist to improve adherence to preventive measures

The medical history should be marked with an alert sticker and a checklist should be included in that history outlining date, type, dose of vaccines and when the next vaccination is due. Anatomical pathologists are encouraged to include a comment on their histology reports on the risk of fulminant sepsis when a spleen is processed, as should a haematologist when HJB are detected.

Registries of patients with asplenia and hyposplenism have been both reported and recommended.^{34,35} The potential role of such ongoing registries is to ensure that patients (and their carers) are given optimal and up-to-date preventive advice, and that they receive long-term ongoing support, such as reminders when revaccinations are due and any new advances in medical care. A registry can also collect important long-term data, may be the vehicle for studies on the long-term efficacy of recommended interventions and is likely to prove cost effective in terms of mortality and rates of OPSI avoided.

Spleen Australia provides educational materials, including alert cards and follow-up of patients with regular reminders about recommended immunisation, as well as provides a clinical resource for healthcare providers and patients. Although currently funded only to enrol patients in Victoria, Tasmania and Queensland, resources are available on the website. Patients registered with Spleen Australia can also access an App for mobile devices for vaccine reminders and additional health tips.

Available resources

Patients' concerns and questions should be raised with the treating general practitioner, and/or treating

specialist or Spleen Australia. Paediatric guidelines are available on the Spleen Australia website (<https://spleen.org.au/VSR/information.html>). Currently available funded vaccines for splenectomised individuals in New Zealand are available on the Immunisation Advisory Centre website <http://www.immune.org.nz/sites/default/files/resources/ProgrammeAspleniaImac20160331V01Final.pdf>.

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