Initial modelling and updates on cost effectiveness from the first 10 years of a spleen registry

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Abstract

Objective: To validate our estimates from our original model and re-evaluate the cost-effectiveness of Spleen Australia, the Australian post-splenectomy registry, using our original model with updated model parameters based on advances in the literature and experience of the registry over the past decade.

Methods: We revisited a decision model from 2005, comparing 1,000 hypothetical registered patients with asplenia or hyposplenism against 1,000 who were not registered, and updated the model parameters. The cost-effectiveness of the registry was evaluated from a healthcare perspective in terms of additional cost per case of overwhelming post-splenectomy infection (OPSI) avoided and as additional cost per life year gained.

Results: Over a cohort lifetime the registry was associated with an additional cost of $125,724 per case of OPSI avoided or $19,286 per life year gained.

Conclusions: Despite our initial over-estimation of immunisation and chemoprophylaxis uptake and increases in unit costs, our re-evaluation confirmed use of the registry to be cost-effective.

Implications for public health: Improved outcomes for patients with asplenia or hyposplenism can be achieved by a cost-effective registry. Additional research into effectiveness of interventions, OPSI prevalence associated with varying intervention use, and compliance rates over time after registration would provide improved accuracy of cost-effectiveness estimates.

Key words: cost-effectiveness, spleen, registry

Our objective was to validate our estimates from our original model[1] and re-evaluate the cost-effectiveness of Spleen Australia, the Australian post-splenectomy registry,[2] using our original model with updated parameters based on advances in the literature and experience of the registry over the past decade.

The spleen has major roles in maintaining red cell integrity and immune function including antibody production and opsonisation of bacteria. Where splenic function is impaired; for example, functional hyposplenism, splenectomy or congenital asplenism, immune function is impaired. This puts the patient at a significant risk of infections including overwhelming post-splenectomy infection (OPSI), malaria, babesia, *Capnocytophagia carnimorsus* and *Bordetella holmesii*.

OPSI is a syndrome of fulminant invasive infection that can lead to death within 48 hours despite aggressive treatment. OPSI has a reported prevalence of 1 in 500 splenectomised patients,[3] with a mortality rate observed to range from 50% to 70%.[4,5] Although international guidelines vary slightly,[2,6-8] overall they address three principles of prevention: immunisation, chemoprophylaxis and patient education. In Australia, Spleen Australia guidelines recommend the following management strategies:[2]

- **Immunisation** – Recommendations include initial and ongoing booster vaccination against *Streptococcal pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* type b (HiB), and annual administration of the influenza vaccination.
- **Chemoprophylaxis** – All patients are recommended daily penicillin or amoxicillin (or a macrolide if allergic) for at least three years after splenectomy, and life-long antibiotics if they are at high risk for infections (e.g. immunocompromised patients). Patients should also carry a supply of antibiotics (commonly, amoxicillin three grams) to use in an emergency in the case of severe illness.
- **Education** – Patients and their family members should be informed about the risk of infections, the importance of immunisations and antibiotics, and the need to present early to medical services in the event of sudden severe illness. Patients should know to seek travel advice prior to travel and be aware of the infectious risk with animal bites. It is recommended that patients always carry a medical alert in the form of a bracelet or wallet-sized card in case they present with illness and an impaired state of consciousness.

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A registry with a key role in improving education, early diagnosis and treatment of OPSI has been suggested to not only reduce rates of infection, but also reduce the mortality risk to 10%[9] by improving the uptake of interventions.[10]

The Spleen Australia registry was established in 2003 as the Victorian Spleen Registry and has since expanded to include Tasmania and Queensland. The primary role of the registry is to reduce the risk of OPSI. To achieve this, patients are contacted upon registration by phone and where possible in person. Registrants receive an education kit in the mail that contains brochures informing them of their risk of infections, the most recent registry newsletter, an alert card, a vaccine record card and a personal immunisation report. Annual newsletters are sent to registrants and their nominated medical practitioner(s). Registrants can also access their personal immunisation report via the Spleen Australia phone application.

In 2005, our group performed a cost-effectiveness analysis of the registry.[1] At the time, the registry had been running for approximately two years with fewer than 250 patients registered with the registry. This model estimated that, although the registry would not be cost-saving (as costs incurred in running the registry are more than those saved from reduced OPSI rates), in the long run (i.e. over the lifetime of the registered population) a registry-based approach was likely to prove cost-effective in terms of cases of OPSI avoided and life years gained. Uncertainty around model estimates revealed that these results were most sensitive to estimates of the rate of OPSI occurrence, the mortality rate following OPSI and the risk reduction generated by preventive interventions. Improving evidence available for these parameters would improve the certainty around future updates of this model.

Our original model highlighted the limited evidence in the field,[1] and little has improved in the intervening decade. Two Australian studies indicated that we initially over-estimated registry and non-registry model parameters.[11,12] We assumed that registrants would have 100% uptake of interventions. A survey of Spleen Australia registrants found that 79% reported booster vaccination, 84% reported annual influenza vaccination and, among participants within their first two years since splenectomy, 83% reported taking antibiotics.[11] A study among non-registered post-splenectomy patients in New South Wales revealed that, despite a high initial vaccination rate (93%), 12% of patients took up ongoing influenza vaccine and 40% used prophylactic antibiotics.[12]

In terms of outcomes, the number of invasive pneumococcal disease (IPD) cases in the asplenic population in Victoria in 2010–2015 ranged from two to nine per annum (mean 5.6).[13] Where vaccination was known, 57% were fully vaccinated and 43% were not. A study in Victoria suggested that registration is associated with a reduction in vaccine-preventable disease rates of 69%.[14] The costs of treating a case of OPSI remains highly variable, with cases notified to Spleen Australia costing up to $280,000 (in 2014).

In 2016, we combined the registry experience to date and findings of the two recent Australian studies[11,12] to update the parameters of our original model[1] and assess implications for effectiveness and cost-effectiveness estimates.

Methods

We performed a cost-effectiveness analysis from a healthcare perspective using a decision tree model with Markov nodes comparing a cohort of 1,000 registry participants to a cohort of 1,000 people with asplenia or hyposplenism not covered by a registry.[1] The Markov nodes are annual health states. Cohort age on entry was set to the mean age of patients registered at the time of initial model construction (48 years). The impact of the registry was assessed through uptake rates of vaccination, chemoprophylaxis and education, on outcomes of OPSI and mortality. Costs and outcomes were evaluated over the initial two years of registration (when costs are expected to be high) and the remaining lifetime of the cohort (approximately 60 years). All costs and outcomes that occur in the future are discounted at 5%, so the expression of costs and outcomes is in terms of their net present values.

Similar to our original model, we chose to focus on OPSI as the primary outcome measure. The model was evaluated for two OPSI-related outcomes: the number of cases of OPSI prevented (the difference in number of cases of OPSI estimated for the cohort with and without a registry) and the number of years of life gained with (compared to without) a registry. This is directly related to the cases of OPSI prevented, as the only sources of mortality in the model cohorts are the background life expectancy (common across the two cohorts) and the mortality following OPSI.

We updated our model parameters to reflect the newly available evidence (see Table 1).[11,12] There is no additional evidence on OPSI risk or the effectiveness of interventions (with or without a registry) on OPSI risk reduction. We retained the model parameters from the initial model for OPSI risk reduction with intervention, as the study performed by El Alfy et al.[15] remains the best available estimate for reduction in OPSI risk with varying uptake of interventions to date (Table 1).

The original estimates of resources required for initial education remained valid and were updated to 2016 Australian dollars to reflect general inflation and current treatment recommendations (Table 1). All cost estimates were based on the costs experienced in the local hospital and costs experienced by the registry. The increased scale of operation of the registry (beyond expectations of the original model) has resulted in greater distribution of annual fixed administration costs ($250,000) distributed among 5,000 participants ($50/participant). Conversely, vaccine costs have increased due to additions to the recommended vaccines. The cost of a treating a case of OPSI was based on local hospital cost data from known OPSI cases. The cost of treating a case of OPSI in hospital remains highly variable and available estimates remain within the original range, so we maintained the original estimate.

Results

Baseline estimates and associated ranges of uncertainty for each required category of model input are shown in Table 1. Cost-effectiveness results are presented in Table 2. Costs and benefits of the registry are shown for both the first two years of implementation and over the lifetime of the cohort (approximately 60 years).

In the first two years, the additional cost of the registry was $211,077 per case of OPSI avoided or $284,846 per life year gained. After this initial registration period the cost-effectiveness improves over time, such that over the cohort lifetime a post-splenectomy register is associated with an additional cost of $125,724 per case of OPSI avoided or $19,286 per life year gained.

Discussion

We now have 10 years of monitoring data for a vastly increased registry cohort that has allowed us to self-evaluate and validate the assumptions of the original model of cost-effectiveness of the Spleen Australia registry.

The most noticeable divergence between the 2005 model and the lived experience of the Spleen Registry was in the scale of operation. The original model was based on a cohort of 1,000 registered participants and included administrative costs based on an expected scale of 500 registry participants and an anticipated general administrative cost of $40,000 per annum. This scale was reached within a few years of the initial model. As of April 2018, there are now more than 7,890 patients enrolled on the registry, with over 1,000 new registrations each year.

Our updated model estimates that use of a spleen registry generates 64 additional years of life for a cohort of 1,000 patients, at a cost of $19,286 per life year gained. There is greater distribution of administration costs with a larger registry cohort, leading to a lower administration cost of $50 per registrant. Due to increased vaccination costs (from general inflation and additions to the management recommendations) and reduced estimates of treatment uptake, the cost of preventing an OPSI case ($105,154 to $125,724 per OPSI case avoided) and the cost per life year gained ($16,113 to $19,286 per life year gained) has increased from our previous estimates, as shown in Table 2. Although the estimated rate of return has increased from $16,113 per life year gained to $19,286 per life year gained, the updated estimated rate of return remains within the range of commonly funded interventions in Australia (up to $60,000 per healthy life year gained).[16]

There have been no studies comparing cost-effectiveness of Australian clinical registries, other than a report by the Australian Commission on Safety and Quality in Health Care that assessed the cost-effectiveness of five Australian clinical registries.[17] This report concluded that these five clinical registries provided significant positive return on investment but declared that not every clinical registry that is established will be cost-effective. In our evaluation, we show that although using this registry is not cost-saving, it does appear to be cost-effective when viewed over a cohort lifetime and is associated with improved patient health benefits.

Table 1: Outcomes and cost estimates in the initial model and updated model.

	Initial Model (2005)		Updated Model (2016)	
	Estimate	Range	Estimate	Range
Uptake of interventions with registry:	100%	100%	84%	80–90%
Uptake rate in absence of registry:				
Vaccination	90%	80–90%	80%	70–90%
Chemoprophylaxis	67%	20–70%	40%	20–70%
Education	22%	10–60%	22%	10–60%
OPSI rate without intervention	0.5%	0.23–0.5%	0.5%	0.23–0.5%
OPSI risk reduction with intervention:				
Vaccination, chemoprophylaxis and education	70%	50–84%	70%	50–84%
Vaccination and chemoprophylaxis	60%	50–73%	60%	50–73%
Vaccination only	50%	50–56%	50%	50–56%
Mortality following OPSI	50%	20–70%	50%	20–70%
Unit cost of:				
Vaccination on entry (all below plus HiB)	$143	$71–$215	$425	$213–$638
Vaccination - influenza (annual)	$30	$14–$43	$25	$13–$38
Vaccination - pneumococcal (every 5 years)	$37	$19–$56	$200	$100–$300
Vaccination - meningococcal (every 5 years)	$30	$15–$45	$200	$100–$300
Chemoprophylaxis (per year of antibiotics)	$172	$86–$257	$200	$100–$300
Education on entry (nurse consultation)	$38	$19–$57	$50	$25–$50
Education (annual communications)	$1	$0.5–$1.5	$1	$0.5–$1.5
Registry administration costs per person	$80	$40–$120	$50	$40–$120
Cost of OPSI case	$50,000	$27,014–$96,513	$50,000	$27,014–$96,513

We initially anticipated this service to be a state-wide registry and evaluated its cost-effectiveness in this scale. In performing this re-evaluation, we realised that not only did we over-estimate compliance to interventions, but we also underestimated the scale and growth of the registry. However, despite inaccuracies in our initial modelling estimates, our results revealed that the initial model accurately predicted that the registry would be a cost-effective intervention.[1] In addition, we chose OPSI as our primary outcome measure. Although OPSI is the most important infectious outcome, risk of other infectious outcomes including but not limited to malaria, *Capnocytophagia carnimorsus* and *Bordetella* holmesii are likely to be reduced with registry use. Thus, limiting our assessment to OPSI as the primary outcome is likely to have missed some benefits of the registry.

Although this re-evaluation has incorporated recent evidence and data, it also highlights the limited breadth and depth of the literature regarding OPSI risk reduction with varying intervention use and the efficacy of such interventions. Estimates of cost-effectiveness remain most sensitive to the accuracy of these efficacy data. We also still have limited data on the proportion of patients with asplenia or hyposplenism who are not registered in Victoria, Tasmania and Queensland. Vaccine uptake rates appear higher among registered cohorts[11] compared to non-registered cohorts,[12] suggesting a mechanism for lower rates of preventable infections in those on the spleen registry.[14]

Conclusions

Use of a registry appears to have a causal impact on increasing compliance rates to management interventions and reduction in adverse infectious outcomes. Our re-evaluation finds that although the registry is not cost-saving, it does appear to be cost-effective.

Table 2: Cost effectiveness of registry in the initial model and updated model.

	Initial Results (2005)	Updated Results (2016)
Cost effectiveness over lifetime perspective		
OPSI cases avoided	12.5 cases (undiscounted 25.6)	9.9 cases (undiscounted 20.2)
Life years gained	81.8 years (undiscounted 242)	64.2 years (undiscounted 191)
Additional costs	$1,319,093	$1,239,544
$ (per OPSI case avoided)	$105,154	$125,724
$ (per life year gained)	$16,113	$19,286
Cost effectiveness over first two years		
OPSI Cases Avoided	1.6 cases	1.2 cases
Life years gained	1.2 years	0.9 years
Additional Costs	$239,036	$258,799
Cost (per OPSI Case avoided)	$152,611/OPSI	$211,077/OPSI
Cost (per life year gained)	$205,911/year	$284,846/year

Implications for public health

Practice recommendations

It is logical to expand the registry to host all states and territories within Australia to optimise uptake of preventive health interventions and thus infectious outcomes in patients with asplenia or hyposplenism, since many of the capital costs of development of intellectual property, online support systems and registry software are fixed. In addition, clinicians should actively register patients with asplenia or hyposplenism to the healthcare service to improve adherence to management and prevention of adverse infectious outcomes.

Research recommendations

Rates of compliance in registrants over time would provide better long-term estimates of effectiveness and cost-effectiveness. In addition, greater precision over estimates of OPSI prevalence with varying levels of uptake of preventive interventions, and the effectiveness of interventions – particularly the use of long-term chemoprophylaxis – would reduce uncertainty over estimates of registry effectiveness and cost-effectiveness.

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