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Cost-effectiveness of meningococcal polysaccharide serogroups A, C, W-135 and Y conjugate vaccine in Australian adolescents

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ABSTRACT

Objectives: The incidence of invasive meningitis disease (IMD) is increasing in Australia. A conjugate vaccine of meningococcal polysaccharide serogroups A, C, W and Y (MenACWY) is currently indicated for infants aged 12 months on the Australian National Immunisation Program. This study sought to determine the cost-effectiveness of a broader MenACWY vaccination program for Australians aged 15 to 19 years.

Methods: A Markov model was constructed to simulate the incidence and consequences of IMD in Australians aged 0–84 years, with follow up until age 85 years. The model comprised four health states: 'Alive with no previous IMD', 'Alive, post IMD without long-term complications', 'Alive, post IMD with long-term complications' and 'Dead'. Decision analysis compared the clinical consequences and costs of a vaccination program versus no vaccination from the perspective of the Australian health care system. Age-specific incidence of IMD and fatality rates were derived from Australian surveillance data. Vaccine coverage, vaccine efficacy and herd immunity were based on published data. The total cost for MenACWY vaccination was AU$56 per dose. Costs and health outcomes were discounted by 5% per annum (in the base-case analysis).

Results: Compared to no vaccination, a MenACWY vaccination program targeted at Australians aged 15–19 years was expected to prevent 1664 IMD cases in the Australian population aged 0–84 years followed up until age 85 years. The program would lead to 1131 life years (LYs) and 2058 quality adjusted life years (QALYs) gained at a total cost of AU$115 million (all discounted values). These equated to incremental cost-effectiveness ratios of AU$101,649 per LY gained and AU$55,857 per QALY gained. A probabilistic sensitivity analysis demonstrated a likelihood of cost-effectiveness of 34.6%, assuming a willingness to pay threshold of AU$50,000 per QALY gained.

Conclusion: The likelihood of this program being cost-effective under a willingness to pay threshold AU $50,000 per QALY gained is 35%.

1. Introduction

Invasive meningococcal disease (IMD) is a rare but serious, unpredictable, and life-threatening infectious disease [1]. IMD mostly occurs in children less than five years of age and during late adolescence (15–19 years), with the highest carriage rates in the latter group [2]. Worldwide, there are 13 known serogroups of Neisseria Meningitidis, but serogroups A, B, C, W, X and Y cause almost all cases of IMD [3].

In Australia, since the introduction of the national meningococcal C (MenC) immunisation program for all children and adolescents aged 1–19 years in 2003, the incidence of IMD has decreased drastically, reaching a nadir of 0.6 per 100,000 (149 cases) in 2013 [4,5]. However, the number of IMD cases has started to increase again since 2014. From 2014 to 2017, the incidence of IMD increased by 167%, reaching 1.6 per 100,000. This increase has been predominantly driven by infections caused by meningococcal W (MenW), which accounted for 37% of all IMD cases in 2017 [6]. MenW is associated with more severe clinical manifestations and a higher case fatality than IMD caused by other serogroups [4,5]. To curb the increasing trend of IMD, the Australian Federal Government added a conjugate vaccine of meningococcal polysaccharide serogroups A, C, W and Y (MenACWY) (Nimenrix), to the National

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Immunisation Program (NIP) for infants aged 12 months in 2018 [7]. The government also recently agreed to fund a MenACWY immunisation program for teenagers and young adults, due to the high carriage rate in this population [7]. (At present, there is no national immunisation program against Men B in Australia.) Existing literature suggests the MenACWY vaccination for adolescents in the US, Canada and the Netherlands is cost-effective [8–10], but there have been no published cost-effectiveness studies from Australia.

In the present study, we estimated the cost-effectiveness, from the perspective of the Australian healthcare system, of a MenACWY vaccination program targeted at Australians aged 15 to 19 years. This work helped to inform the recent decision by the Australian government to fund the program.

2. Methods

2.1. Model structure

A decision analytic Markov model was developed to compare the cost-effectiveness of delivering a single dose MenACWY vaccine to Australians aged 15–19 years versus no vaccination. The model was designed to capture the key clinical outcomes of the immunisation program: non-fatal incident IMD, fatal incident IMD and non-fatal IMD cases that led to long-term complications. Therefore, the model comprised four health states: 'Alive with no previous IMD', 'Alive, post IMD without long-term complications', 'Alive, post IMD with long-term complications' and 'Dead' (from either IMD or other causes) (Fig. 1). The cycle length was one year. The model did not explicitly capture recurrent IMD among survivors of IMD, regardless of whether or not they suffered long-term complications. The analysis was conducted from the perspective of the Australian health care system. The model's baseline year was 2018, and a 5% annual discount rate was applied to both cost and outcomes including life years lived and quality adjusted life years (QALYs) lived, as recommended by the Australian guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) [11].

2.2. Model population

The model population comprised the Australian population aged 0 to 84 years in 2016, stratified into 5-year bands [11]. Follow-up was simulated until death or age 85 years. All subjects started the simulation in the health state 'Alive, no previous IMD'.

2.3. Model inputs

All data inputs were drawn from publicly available sources and are summarised in Table 1 and Appendix 1. The age-specific incidence of IMD (without vaccination) and mortality rates were obtained from Australian national statistics (Appendix 1) [6]. We assumed subjects in the health state 'Alive, post IMD without long-term complications' had the same probabilities of death as subjects who had never had IMD, while subjects in the health state 'Alive, post IMD with long-term complications' carried an increased risk of death. We derived the relative mortality ratio (RMR) of IMD patients with complications from a Danish national cohort study reporting long-term mortality among IMD survivors [12]. The occurrence of long-term complications by types and their severity were derived from a South Australian study reporting the occurrence and manifestations of IMD complications among children [13].

2.4. Costs

In the base-case scenario, we applied a vaccination cost of AU $46 per MenACWY vaccine and administration cost of AU$10 [14], which is generally consistent with the estimated administration costs of $11 for a school-based vaccination program (information provided by Ms. Sue Campbell-Lloyd from the immunisation unit of Health Protection NSW in October 2017). The costs of acute IMD events were derived from data regarding Australian Refined-Diagnostic Related Groups (AR-DRGs) [15]. The unit costs of the various long-term complications of IMD were drawn from a Canadian study [16]. Canadian dollar values were converted to the Australian dollars by applying a conversion rate of 1.02, effective as of 2012. By applying the complication-specific annual health care costs [16] to the distribution of long-term complications [13], we were able to calculate the weighted average annual cost for long-term complications after IMD. All health care costs were converted to Australian dollars and inflated to 2018 values using the Health Price Index published by the Australian Institute of Health and Welfare [17]. Conversion rates from Australian dollars to US dollars and Euros were 1:0.7406 and 1:0.6326, respectively, as of 30th June 2018.

2.5. Utilities

Age-specific utility norms were derived from the 2007 Australian national survey of mental health and well-being (which used the AQoL-4D quality of life tool) [18]. We did not apply further disutility among patients who survived IMD without

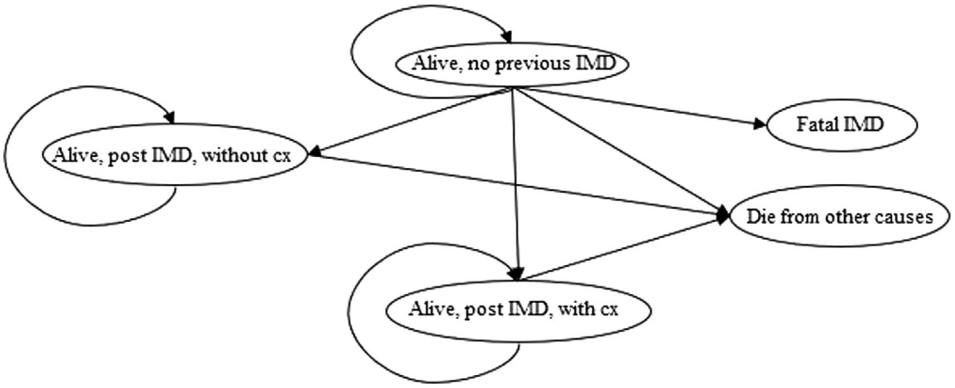

Fig. 1. Model structure. IMD = invasive meningococcal disease, 'without cx' = without long-term complications, 'with cx' = with long-term complications.

Table 1
Model inputs.

Input variables	Inputs	Range/Standard Error	Distribution	Source
IMD with complications	37.60%	28.5–47.4%	Beta	[13,23]
RMR (IMD with complications)	1.21	1.06–1.37	Lognormal	[12]
Baseline Utility			Beta	[18]
0–19 years	0.87	0.86, 0.88		
20–29 years	0.86	0.85, 0.87		
30–39 years	0.84	0.83, 0.85		
40–49 years	0.81	0.80, 0.82		
50–69 years	0.80	0.78, 0.81		
70–79 years	0.76	0.76, 0.79		
80 + years	0.70	0.67, 0.73		
IMD complication type				
Minor, single	14.6%		Dirichlet	[24]
Minor, multiple	4.9%			
Major, single	26.8%			
Major, multiple	53.7%			
Utility decrement				
Minor, single	0.06	0.01	Beta	[19]
Minor, multiple	0.12	0.01		
Major, single	0.14	0.01		
Major, multiple	0.39	0.02		
Long-term cost per annum (complicated IMD)				
Minor, single	$1512	25% variance	Uniform	[24]
Minor, multiple	$3753			
Major, single	$10,742			
Major, multiple	$18176			
Hospitalisation cost				
Acute (death/complicated)	$24,453	25% variance	Uniform	[15]
Acute (non-complicated)	$7432			
Vaccine price	$46			
Administration cost	$10	$8, $12		[14]
Vaccine efficacy	0.956	0.941, 0.967	Beta	[25–35]
Herd effects (relative risk)	0.33	0.23, 0.48	Beta	[9]
Coverage				
School-based program	80%	66.9%, 90.4%	Beta	[20]
GP-based program	22%	10.4%, 36.3%	Beta	[21]

IMD: invasive meningococcal disease; RMR: relative mortality ratio.

long-term complications, while disutilities associated with the long-term complications of IMD were derived from a survey of parents' preference for paediatric health outcomes [19]. Similar to long-term costs, by applying the complication-specific disutilities [19] to the distribution of long-term complications [13], we were able to calculate the weighted average long-term disutility for long-term complications after IMD. These were then applied to age-specific utility norms to derive utilities for people with long-term complications from IMD.

2.6. The efficacy of the vaccination program

The proposed vaccination program targets Australians aged 15–19 years via a school-based program for the 15–17 year-olds and a GP-based program for the 18–19 year-olds. In the base-case model, we assumed 80% coverage of the school-based program [20] and 22% coverage of the GP-based program [21].

Vaccine effectiveness (VE) data were extrapolated from the reported immunogenicity data from systematic review and meta-analysis of literature (Appendix 2). We further assumed 5% waning in VE per annum for four years, followed by 50% waning per annum in perpetuity. This assumption was based on advice by Australian Technical Advisory Group on Immunisations (ATAGI) (personal communication).

The extent of herd immunity effects was obtained from a UK study (Table 1) [22]. We assumed the attainment of full herd immunity effects within 10 years, after which herd immunity effects remained constant for another seven years, before waning to zero effects over another 10 years. This assumption was endorsed by ATAGI.

2.7. Scenario analyses

Scenario analyses were applied using the following parameters:

- follow-up to a maximum of 90, 95 and 100 years
- linear increase in the background incidences of IMD from Year 2 to Year 5 until they peaked at 10%, 25% and 50% greater than the baseline year, beyond which background rates remained constant
- waning VE of 50% per annum from Year 2 to 5
- herd immunity attainment and waning period (the attainment of full herd immunity effects within 5 years, after which herd immunity effects were remained constant for another 13 years, before waning to zero effects over another 5 years)
- annual discount rate of 3.5% per annum

2.8. Sensitivity analysis

Deterministic sensitivity analysis (DSA) was applied to capture and compare the uncertainties around key input variables under the base-case scenario one at a time. The variance and limits of the input variables are summarised in Table 1. The results are presented in a tornado graph (Fig. 2). A probabilistic sensitivity analysis (PSA) was further applied by assigning probabilistic distributions to all key input variables (Table 1) and undertaking a Monte Carlo simulation with 1,000 iterations. The results are

summarised using the cost-effectiveness acceptability curve (CEAC) (Fig. 3).

The model was developed using Microsoft Excel 2013.

3. Results

3.1. The effectiveness of the MenACWY vaccination program

Under the base-case scenario, the proposed vaccination program was expected to prevent 1664 IMD cases in the Australian population aged 0 to 84 years, if they were followed up until age 85 years, including prevention of 138 fatal IMD cases, 951 IMD cases with long-term complications and 574 IMD cases without long-term complications (Table 2).

3.2. Base-case cost-effectiveness analysis

The net cost of the proposed MenACWY vaccination program was AU$328,397,835 (discounted), with a total health benefit of 1131 life years (discounted) and 2058 QALYs (discounted) gained. Therefore, the estimated ICERs were AU$101,649 per Life Year (LY) gained and AU$55,857 per QALY gained (Table 2).

3.3. Scenario analyses

The results of scenario analyses are summarised in Table 3. Follow-up until 90, 95 and 100 years improved the cost-effectiveness of the vaccination program, as did a higher assumed background incidence of IMD. A 10% increase in background IMD incidence in the first five years would lead to ICERs of AU$86,802 per LY gained and AU$47,692 per QALY gained. If it was assumed that full herd immunity would be attained in 5 years instead of 10, the ICERs dropped to AU$86,519 per LY gained and AU $46,965 per QALY gained. Finally, with an assumed annual discount rate of 3.5%, the ICERs were AU$62,291 per LY gained and AU$34,580 per QALY gained.

3.4. Sensitivity analyses

In the DSA, the model was most sensitive to (1) the risk of long-term complications, (2) the level of herd immunity, (3) the coverage of school-based immunisation program, and (4) annual cost of long-term complications (Fig. 2).

Under the base-case scenario, the PSA yielded a mean ICER of AU$56,524 per QALY gained (95% confidence interval: AU$31,222 to AU$87,930 per QALY gained). The likelihood of cost-effectiveness was 34.6%, assuming a willingness to pay threshold of AU$50,000 per QALY gained (Fig. 3).

4. Discussion

Our findings indicate that a MenACWY immunisation program targeted at Australians aged 15 to 19 years would be expected to prevent 1664 IMD cases among the Australian population aged 0 to 84 years, if followed up to age 85 years, at a total cost of AU $115 million. The associated ICER was AU$55,857 per QALY gained. The incidence of IMD, risk of IMD complications and level of herd immunity exerted the greatest impact on the cost-effectiveness evaluations. In the PSA, the probability of MenACWY being cost-effective at a willingness to pay threshold of AU$50,000 per QALY gained was around 35%.

Adolescents and young adults, serving as carriers for meningococcal disease, play a critical role in the epidemiology of IMD [2]. A few studies have evaluated the cost-effectiveness of MenACWY

Table 2
Base-case results for MenACWY vaccination versus no vaccination.

	Comparator	Nimenrix	Difference	ICER
IMD	7980	6316	−1664	
IMD without complications	4575	3624	−951	
IMD with complications	2759	2185	−574	
Fatal IMD	646	508	−138	
Cost (discounted)	$213,459,655	$328,397,835	$114,938,180	
YLLs (discounted)	393,737,638	393,738,769	1131	$101,649
QALYs (discounted)	320,720,147	320,722,205	2058	$55,857

IMD: invasive meningococcal disease; YLL: years life loss; QALY: quality adjusted life year; ICER: incremental cost effectiveness ratio.

Table 3
Results of scenario analysis for MenACWY vaccination versus no vaccination.

Scenarios	Diff. YLL	Diff. QALY	$/YoLS	$/QALY
Base case	**1131**	**2058**	**$101,649**	**$55,857**
Maximum age of follow-up				
Follow-up until age 90 years	1223	2181	$90,799	$50,923
Follow-up until age 95 years	1279	2245	$85,580	$48,763
Follow-up until age 100 years	1299	2264	$84,054	$48,220
Increasing IMD incidence				
10% increase in IMD incident rate in Yr2-Yr5, then plateau	1237	2251	$86,802	$47,692
25% increase in IMD incident rate in Yr2-Yr5, then plateau	1396	2541	$68,765	$37,775
50% increase in IMD incident rate in Yr2-Yr5, then plateau	1661	3025	$46,384	$25,475
VE waning				
Waning vaccine effectiveness: 50% per year in Yr2-Yr5; zero from Yr6	1043	1920	$114,277	$62,058
Herd Immunity attainment and waning				
Herd immunity: 67% reduction in IMD by Yr5 (and 5-yr wane)	1288	2262	$86,519	$46,965
Annual discount rate				
3.5% annual discount	1632	2940	$62,291	$34,580

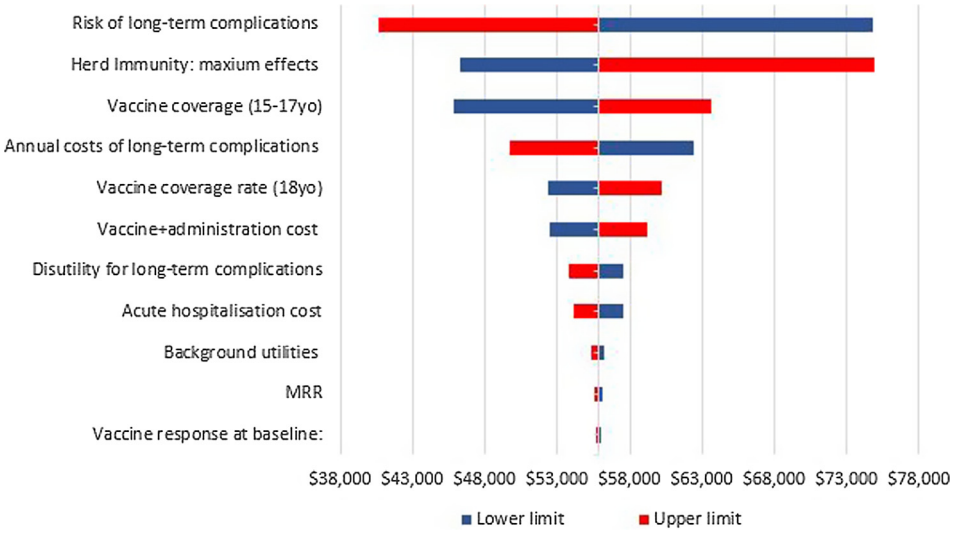

Fig. 2. Tornado graph of deterministic sensitivity analysis.

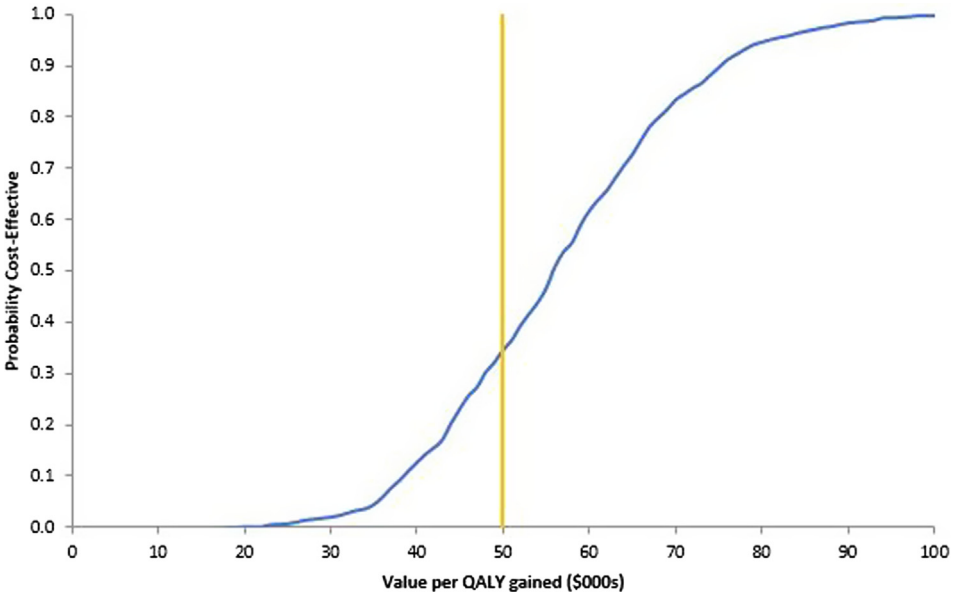

Fig. 3. The cost-effectiveness acceptability curve for the teenager and young adults MenACWY vaccination program.

immunisation programs for teenagers [8–10], but this is the first in Australia. A Canadian study concluded that a MenACWY immunisation program at 12 years of age would reduce IMD incidence by 78% at a cost of CA$31,000 per QALY gained [9]. A US study compared a MenACWY immunisation program in toddlers and adolescents and concluded that the adolescents program was more likely to be cost-effective [8]. A study from the Netherlands predicted that while MenACWY immunisation at 14 months would be cost-saving, the cost-effectiveness of a booster dose at 12 years was largely dependent on the level of remaining herd immunity in the population [10]. Despite a wider age group being targeted (15–19 years), our findings are largely consistent with the results of other studies. As with the other studies, our model was sensitive to the background incidence of IMD, the occurrence of long-term complications, the level of herd immunity, and the price of the MenACWY vaccine.

In the base-case model, we assumed the age-specific IMD incidence remained unchanged throughout the entire time horizon. This is likely to be a conservative assumption when there is no evidence suggesting a reversal of the recent trend of increasing IMD incidence [6]. As shown in the scenario analysis, even a slight increase in background IMD incidence (linear increase of 10%, 25% and 50% over 5 years and plateauing afterwards) substantially improved the ICERs of the immunisation program. To estimate the risks of long-term complications among IMD survivors, we used data from a South Australian case series study of infants and children [13]. However, due to relatively small sample size (109 cases in total), the estimates were subject to high uncertainty. Nonetheless, these were the most relevant Australian data to inform the occurrence of long-term complications following IMD. Additionally, since we applied the same risk of complications to all surviving IMD patients in the model, it was likely that we underestimated the occurrence and the severity of long-term complications in adults and older patients, who are generally at higher risks of long-term sequelae after IMD than infants and children [36,37]. Therefore, the ICERs were likely to be overestimated.

Herd immunity is another key determinant in the cost-effectiveness evaluation of MenACWY vaccine in teenagers and young adults. Consistent with other modelling studies [9,38,39],

we applied a maximal herd immunity effect of 67% in our model, which is attainable with approximately 80% coverage of vaccination in the target population [22]. We assumed an 80% coverage in the school-based program for the base case analysis. Increasing coverage beyond 80% without assuming any further increase in herd immunity would increase the cost-effectiveness ratio (as shown in our sensitivity analysis), because costs would increase to a greater extent than benefits. Besides the magnitude of herd immunity, the time to attain herd immunity was also influential in the cost-effectiveness evaluation. In the base-case scenario, we assumed that maximal herd immunity was reached by Year 10, maintained until Year 17 (to reflect the time period of the immunisation program), and then waned from Year 18 over another 10 years. This was a conservative assumption compared to other modelling studies [9], as well as the experiences of the MenC vaccination catch-up program introduced in Australia in 2003. Following the MenC catch-up program in 2003, the incidence of MenC IMD declined by over 10 fold in just five years, largely related to herd immunity [6].

From a practical point of view, the major challenge of adolescent immunisation programs is the attainment of high coverage to confer herd immunity. In the base-case analysis, the estimated coverage rate (80%) from the school-based program was based on: (i) current uptake rates of the first human papillomavirus (HPV) vaccine among 15 year-olds [40]; (ii) the historical rates of pertussis immunisation uptake when offered to school students aged 14–16 years (Year 9 or 10) [41]; and (iii) the uptake of Meningococcal C vaccine by Year 10 students during a 2003–2004 program in the Australian state of New South Wales [20]. The reported uptake rates of these vaccines differed by gender (for HPV) and State (for pertussis) but ranged from 62% to 86%. An estimated uptake of 80% for MenACWY immunisation was considered reasonable given the exposure to the publicity and their knowledge about IMD being a vicious infectious disease. For the GP-based program for those aged 17–19 years, we applied a lower coverage rate based on a general-practice based MenC immunisation program in Australia [21].

Cost-effectiveness analyses of health interventions in Australia typically adopt a default willingness to pay threshold of AU $50,000 per QALY gained, but the actual threshold for decision-making depends on many other factors, including the budget impact, the availability of alternative interventions, and the severity and social impact of diseases [42].

A few limitations of our study warrant mention. First, as mentioned in the above, some of the key input variables were subject to uncertainty. However, the impact of major uncertainties was examined in the scenario and sensitivity analyses. Secondly, our economic evaluation did not consider the societal impact of acute and long-term complicated IMD on patients and their family. The adoption of a societal perspective would further improve the cost-effectiveness of the vaccination program, especially given that IMD affects a young population. Finally, the results of our study may not be generalisable to countries other than Australia, which has a universal healthcare system. Nonetheless, our main finding that a MenACWY immunisation program targeted to Australians aged 15 to 19 years is likely to be cost-effectives is in accord with the conclusions of studies from other markets.

5. Conclusion

To our knowledge, this is the first published economic analysis of MenACWY immunisation program targeted at Australians aged 15 to 19 years. The probability of this program falling below a willingness to pay threshold of AU$50,000 per QALY gained was 35% with the current study assumptions.

Acknowledgement

DL, SS, EZ, SF and JL conceived and designed the study; DL, SS and EZ developed the model; DL, SS and EZ performed the analysis of the data. All authors provided critical input on the interpretation of study results.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.07.008.

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