PHARMAC
Pharmaceutical Management Agency

PTAC IMMUNISATION SUBCOMMITTEE MEMORANDUM

From: Medical Director

Date: April 2018

Meningococcal disease cover paper

PURPOSE OF THIS PAPER

This paper outlines the meningococcal vaccine papers that the Immunisation Subcommittee will review at this meeting and provides the commercial context for considering meningococcal B and C vaccines. The Factors for Consideration as they relate to meningococcal disease are addressed in the individual papers for B and C vaccines respectively.

DISCUSSION

PHARMAC intends to issue an RFP for the supply of various immunisation schedule vaccines in late 2018. Contracts awarded as a result of the RFP will be for supply of vaccines commencing from July 2020. PHARMAC now seeks advice from the Subcommittee about the types of vaccines and possible eligibility criteria for meningococcal vaccines to inform the RFP process and subsequent contracting negotiations and funding decisions.

The Subcommittee's advice will be used to determine which, if any, meningococcal vaccines might be included in the RFP, and for which eligible groups. PHARMAC would then make any decisions regarding the funding of vaccines or eligible groups following the analysis of bids received in the commercial process, pending available funding. Funding decisions of the RFP for listing from July 2020 would likely be made by July 2019.

Meningococcal C vaccines

In February 2014, the Subcommittee considered a paper initiated by PHARMAC staff about meningococcal C vaccine eligibility (paper provided in Meningococcal C Appendix 1, Subcommittee minutes in Appendix 2). The Subcommittee deferred making a recommendation on widening access to meningococcal C vaccines, instead recommending that PHARMAC staff assess the effects of funding a meningococcal C vaccination programme for people in close living situations such as prisons, barracks, university halls of residence and those boarding at boarding schools, as well as for universal vaccination of infants and adolescents or teenagers, particularly instituted with a catch-up programme.

The meningococcal C analysis paper presents the analysis that the Subcommittee requested in February 2014, looking at the modelling and costs of vaccination in several possible funding scenarios: people in close living situations and universal childhood vaccination of infants, toddlers or teenagers, and catch up options for these.

Meningococcal B vaccine

GSK submitted a funding application for Bexsero meningococcal B vaccine in January 2018 for universal infant vaccination. This funding application will be considered by the Subcommittee at this meeting and will then be subsequently reviewed by PTAC at a later date, likely once the product is Medsafe approved in late 2018 or early 2019.

Costs and Savings

Health-related costs and savings to the person, their family, whānau and wider society

Bexsero is currently available for private purchase for those patients not eligible for funded vaccination.

Delivery of vaccine typically requires GP consultation, vaccination purchase and administration (e.g. nurse). Should any sub-populations or all the relevant populations be provided access through the NIS as proposed by the RFP, they would incur no vaccination dose or administration costs should their administration coincide with the existing timelines of the NIS.

With the 2+1 dosing schedule for infants, the primary doses are aligned with the current National Immunisation Schedule (NIS), but the 12-month booster would be an additional visit which would result in additional work for vaccinators and increased vaccination claim costs for the Ministry of Health. The booster vaccination could be given at 15 months to align with the NIS, but this would mean five injections would be given at the 15 months visit under the current schedule. The base case analysis here assumes an additional vaccine administration cost for the booster dose.

Similarly, for the catch-up dosing of high-risk individuals, additional vaccine administration costs are dependent on timing with respect to the NIS. For the purposes of budget impact assessment, it is assumed the dose is not aligned with the NIS.

Although data on current private purchases of Bexsero has not been found, PHARMAC staff anticipate current uptake of such vaccines to be minimal.

Costs and savings to pharmaceutical expenditure

Analysis here focuses on distinct population considerations reflecting vaccination population scenarios proposed for funding following the Request for Proposal (RFP) released by PHARMAC in December 2018:

a) A universal 2 + 1 vaccination for infants. The 2+1 dosing schedule has the primary administrations at 3 weeks and 5 months and a booster at 12 months.

b) High-risk individuals, reflecting those as defined already on the Pharmaceutical Schedule (e.g. those with compromised immune systems). Patients in the defined sub-populations are all older than 12 months. They would have only one dose.

It should be noted consideration of the universal infant vaccination includes options where 'catch-up dosing' for these high-risk individuals may be included in the overall proposal. If they were, they would adopt the unit price of the Proposal.

Following the RFP, PHARMAC is considering pricing proposals as follows for Bexsero 4CMenB (**Table 1**).

***Please note that all vaccine price information is <u>confidential</u> and not to be shared outside the Committee. ***

Table 1 Proposed Vaccination Schedules and Pricing from PHARMAC RFP

Vaccination schedule	Price per dose
High risk individuals only (enclosed living populations including boarding school dormitories, university residences, prisons and barracks)	s9(2)(b)
2+1 dosing schedule for universal vaccination +/- catch up (proposal 1)	s9(2)(b)
2+1 dosing schedule for universal vaccination +/- catch up (proposal 2)	s9(2)(b)

Source: PHARMAC files (**confidential**).

Estimated Patient Populations

For infants, the estimated population is approximately 61,000. This figure may vary annually based on the changing birth rate, however it reflects a reasonable average yearly estimate. (Source: Stats NZ, August 2018 (http://archive.stats.govt.nz/infoshare/ViewTable.aspx?pxID=1f01ca00-da2d-4805-a7ea-96a0388966e2).

For those high-risk individuals as currently defined by the Pharmaceutical Schedule PHARMAC staff expect the population to be minimal.

Cost per patient

Vaccination costs

As above, cost per patient would differ by vaccine and patient population. It should be noted that should a catch-up program be incorporated into either of the '2+1' dosing schedule proposals, s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j)

Cost per patient consists of both initial dose(s) and booster dose(s) as appropriate:

a) A universal 2 + 1 vaccination for infants. The 2+1 dosing schedule has the primary administrations at 6 weeks and 3 months and a booster at 12 months. By proposal:

   i) Proposal 1: s9(2)(b)(ii), (i.e., 3 x s9(2) per dose). Should high risk individuals be incorporated into this proposal they would cost s9(2)(b) (i.e., 1 x s9(2) per dose).

   ii) Proposal 2: s9(2)(b)(ii), (i.e., 3 x s9(2) per dose). Should high risk individuals be incorporated into this proposal they would cost s9(2)(b) (i.e., 1 x s9(2) per dose).

b) High-risk closed living individuals only, (i.e., defined sub-populations requested to be looked at by the Immunisation Subcommittee (people in close living situations such as prisons, barracks, university halls of residence, and those boarding at boarding schools) – coverage primarily of those 13 to 19)). As a stand-alone proposal, they would cost s9(2)(b) (i.e., 1 x s9(2) per dose).

***Please note that all vaccine price information is confidential and not to be shared outside the Committee. ***

Vaccine Administration Costs

Administration of the base vaccinations for infants is assumed to coincide with the NIS, there are no additional administration costs. Administration of the booster dose for infants and the dose for high-risk individuals assumes an administration cost of $7 (reflecting its administration along with other NIS vaccinations as part of creation of an additional timepoint on the NIS at 12 months) and $20 per dose respectively.

Estimated Incremental Total Cost of Listing

Combined Pharmaceutical Budget (CPB) and DHB cost impact over the first five years of implementing the vaccination program has been estimated for the populations defined above. Note the NPV totals reflect discounting at 8% per annum.

For the purposes of analysis by PHARMAC staff, uptake reflects feedback from the Immunisation Sub-committee in May 2018 on the specified sub-populations:

- 90% (for all doses) for infants (i.e., < 12 months) and high-risk individuals. NIS full coverage targets for infants/children are typically 95%, but data from Ministry of Health as at March 2018 shows this has not quite been achieved (12-month completion is estimated at 93.6%, 24-months at 92%). This is also the assumption used by the supplier in their 2018 submission to PHARMAC.

For ease of comparison **Table 4**, summarises final estimated incremental costs of living for all proposals for all populations, reflecting inclusion/exclusion of High-Risk Closed Living Sub-Populations.

Universal Vaccination Program for Infants: Proposal 1

Table 2 summarises the estimated annual CPB and DHB budget impacts of universal vaccination of infants under Proposal 1. Note the first two doses are assumed to incur no vaccine administration costs, but that the booster dose (in the following year) is assumed to. Over five years, the estimated NPV DHB impact would be approximately s9(2)(b) (s9(2)(b) CPB).

Table 2 Estimated CPB and DHB impact of immunising infants (0 to 12 months) under '2+1' Proposal 1

Item	Year 1	Year 2	Year 3	Year 4	Year 5
Patients (90% uptake)	54,000	54,000	54,000	54,000	54,000
Vaccination Costs					
First dose	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Second dose	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Booster (2nd year)		s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Total CPB impact	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Administration Costs					
First/Second/Booster dose		$1,080,000	$1,080,000	$1,080,000	$1,080,000
Total DHB impact	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),

Notes: Yearly amounts are undiscounted. Uptake reflects likely uptake estimated provided by Immunisation Sub-committee in May 2018 for infants. Analysis assumes vaccine cost of approximately s9(2) No administration costs for the first two doses

are assumed based on scheduling being in line with the New Zealand NIS; it is assumed the booster dose incurs a marginal administration cost ($7) reflecting the creation of a new time point on the NIS.

Universal Vaccination Program for Infants: Proposal 2

Table 2 summarises the estimated yearly CPB and DHB budget impacts of universal vaccination of infants under Proposal 2. Note the first two doses are assumed to incur no vaccine administration costs, but that the booster dose (in the following year) is assumed to. Over five years, the estimated NPV DHB impact would be approximately s9(2)(b) (s9(2)(b) CPB).

Table 3 Estimated CPB and DHB impact of immunising infants (0 to 12 months) under '2+1' Proposal 2

Item	Year 1	Year 2	Year 3	Year 4	Year 5
Patients (90% uptake)	54,000	54,000	54,000	54,000	54,000
Vaccination Costs					
First dose	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Second dose	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Booster (2nd year)		s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Total CPB impact	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Administration Costs					
First/Second/Booster dose		$1,080,000	$1,080,000	$1,080,000	$1,080,000
Total DHB impact	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),

Notes: Yearly amounts are undiscounted. Uptake reflects likely uptake estimated provided by Immunisation Sub-committee in May 2018 for infants. Analysis assumes vaccine cost of approximately s9(2) No administration costs for the first two doses are assumed based on scheduling being in line with the New Zealand NIS; it is assumed the booster dose incurs a marginal administration cost ($7) reflecting the creation of a new time point on the NIS.

Summary

For ease of comparison, **Table 4** summarises all proposals for all populations, reflecting inclusion/exclusion of High-Risk Closed Living Sub-Populations.

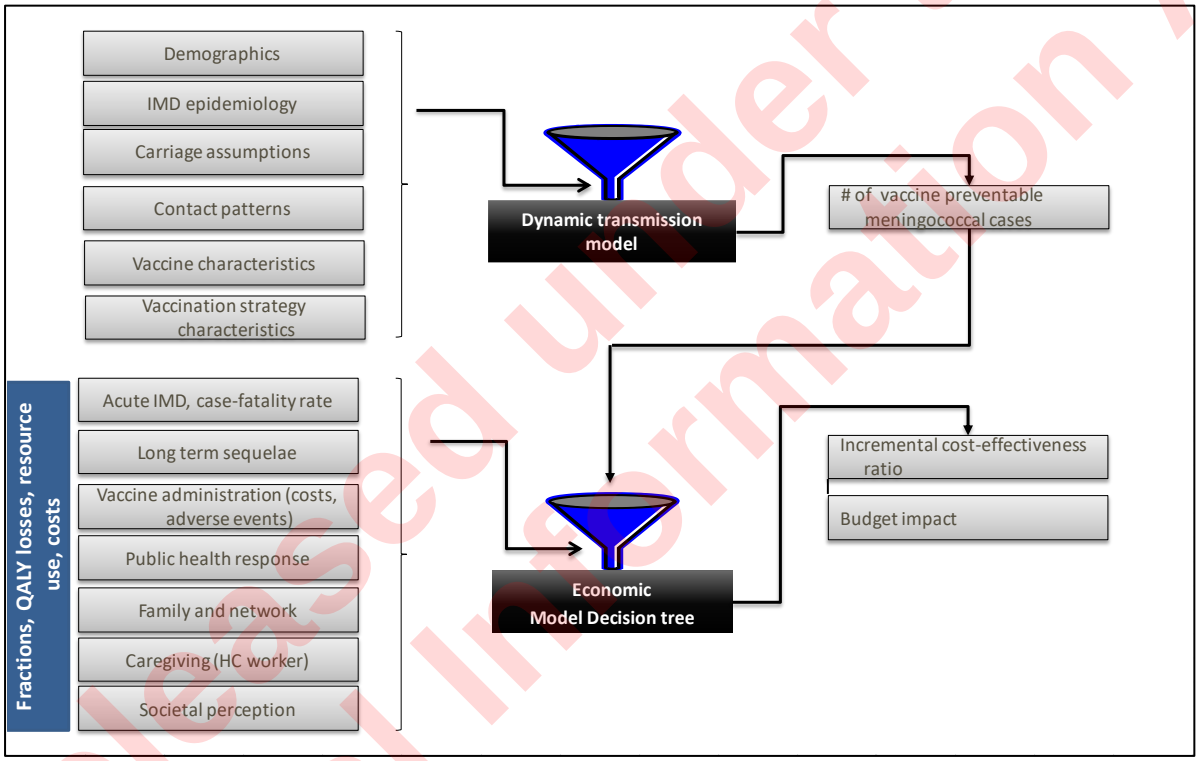
Table 4 Summary: Comparison of Total 5-year NPV CPB and DHB impact of funding Bexsero for defined populations

Vaccination schedule	Total Projected 5-year NPV DHB impact
High risk individuals only (enclosed living populations including boarding school dormitories, university residences, prisons and barracks) - s9(2 per dose	
2+1 dosing schedule for universal vaccination without catch up for high risk individuals (proposal 1) - s9(2 per dose	s9(2)(b)
2+1 dosing schedule for universal vaccination with catch up for high risk individuals (proposal 1) - s9(2 per dose	
2+1 dosing schedule for universal vaccination without catch up for high risk individuals (proposal 2) - s9(2 per dose	s9(2)(b)
2+1 dosing schedule for universal vaccination with catch up for high risk individuals (proposal 2) - s9(2 per dose	

Cost Effectiveness (combining the Health Benefits and Costs quadrants)

The supplier submitted a cost-effectiveness assessment as part of their submission to PHARMAC in 2018. It uses a dynamic transmission model, which aims to model the number of vaccine preventable IMD cases with reference to the dynamic interaction between relevant patient population demographics, IMD epidemiology, carriage, population contact and the effect of the vaccine itself to determine like preventable cases. Concurrently, the model overlays associated resource, cost and health consequences to determine ultimate incremental cost effectiveness and budget impact. **Figure 1** summarises the high-level model structure.

Figure 1 Supplier Economic Evaluation Model Structure



In developing the model, the supplier undertook a systematic literature review to identify all economic evaluations of IMD and all relevant IMD serotypes including those specifically for the MenB vaccination. The model is in line with other health economic evaluations of a meningococcal B vaccine using dynamic transmission models. The model has been previously used by the supplier and accepted in many other countries including the UK and Australia and has been adapted for New Zealand in this analysis.

PHARMAC staff have reviewed the overall structure and deem it conceptually appropriate. However, the actual operational model presented as part of the submission is ultimately deemed unfit for PHARMAC's purposes. A thorough review of the model was undertaken by PHARMAC staff and numerous issues were noted. Ultimately, key issues that affect its viability:

- While acknowledging the inevitable complexity of modelling infectious diseases, the model is of extremely large size and of great difficulty to navigate. While quite detailed in explaining its operation, presented in Microsoft Office Excel software, it takes significant time to operate.
- The model is ultimately a 'black box', i.e., it uses hard coded 'behind the scenes' programming instructions to turn model inputs into final results. This means that while inputs and final outputs are visible, the user is unable to trace in between how inputs are 'converted' by the model into final results.

This model therefore does not readily adhere to PHARMAC's *Prescription for Pharmacoeconomic Analysis (PFPA) Guidelines for Economic Evaluation* (i.e., "Models should avoid unnecessary complexity and should be transparent, well described and reproducible").

On the other hand, the suppliers' own estimate of cost-effectiveness s9(2)(b)(ii), The supplier submission estimates the cost per QALY of the infant '2+1' program at between s9(2)(b)(ii), and s9(2)(b)(ii), (or s9(2) to s9(2) QALYs per $1m). PHARMAC staff, testing this result by using the model (assuming for this purpose it is relatively valid in translating inputs into final results), including by careful review of input values and assumptions, believe the likely true value of the base case (i.e., excluding any cross-protection benefit afforded for Meningococcal W) to be closer to s9(2)(b) QALYs per $m. This is based on a per dose price of s9(2)(b) .

Results are sensitive to varying degrees to assumptions regarding dose cost, incidence (including the proportion of Meningococcal cases that are serogroup B), the case fatality ratio (CFR), sequelae incidence and costs, assumptions about quality of life impact, demographic case distribution, inclusion of cross-protection for meningococcal W and discounting. Assuming a combination of highly favourable assumptions, PHARMAC staff estimate cost-effectiveness may at best reach between s9(2)(b) QALYs per $m (i.e., s9(2)(b)(ii), to s9(2)(b)(ii), per QALY). It should be noted that should per dose price be reduced s9(2) (i.e., to s9(2)(b)), cost-effectiveness would be approximately s9(2)(b)(ii), per QALY or s9(QALYs per $1m.

PHARMAC staff have compared this result with that in studies and as evaluated by other international agencies. Studies quoted in the supplier submission note QALYs per $m estimates ranging from 1.2 (Lecocq et al 2016) to 3.2 (Christensen et al 2014) for a '2+1' infant scheme. PHARMAC staff have also considered the commentary of the UK's Joint Committee on Vaccination and Immunisation (JCVI) in 2014, particularly its conclusions regarding its deliberations on the cost-effectiveness of using serogroup B meningococcal (MenB) vaccine in the UK, both routinely in infants and in at-risk groups. Following iterations of analysis performed based on JCVI feedback, it concluded, "*The consensus of the Committee was that whilst uncertainty remained, and whilst in some scenarios the vaccine would not be cost-effective at a positive vaccine price, the results of the final iteration of the cost-effectiveness model indicated that for an infant programme, in the scenarios considered most plausible by the Committee, the vaccine was still cost effective (at a very low positive price)*."

Whilst the JCVI did not publicly disclose what such a price would be or what it deemed 'cost-effective', it is noted that generally speaking UK's National Institute for Health and Care Excellence (NICE) has a general cost per QALY threshold for acceptability of decisions of approximately £30,000 per QALY. It should be noted that final analysis incorporated revisions suggested by the JCVI including:

- Inclusion in the base case model of a quality of life adjustment factor (QAF) of 3 agreed by the JCVI in June 2013 (as opposed to this being accounted for in an additional analysis as had been done previously);
- Inclusion of a proportion of litigation costs associated with meningococcal disease in the NHS
- Inclusion of quality of life losses to family members.

It should be noted that none of these are in accordance with PHARMAC PFPA Guidelines for Economic Evaluation. PHARMAC staff in particular tested the impact of using a QAF in the supplier model and noted that by itself it considerably improved the cost-effectiveness of final outcomes.

Finally, PHARMAC staff considered the feedback of the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, which has previously considered Bexsero. In November 2013, a major submission requested the inclusion of 4CMenB in the Australian National Immunisation Program (NIP) with a proposed vaccination schedule of 3+1 in infants, a two-dose course in adolescents and a catch-up programme in older infants, toddlers and adolescents. The submission presented an incremental cost per QALY between AU$45,000 and AU$75,000 per QALY (i.e., 13 to 22 QALYs per $1m). The PBAC expressed several concerns including:

- lack of direct evidence of vaccine efficacy against infection and disease
- lack of evidence demonstrating ability of vaccine to generate a population level protective herd immune response
- increasing uncertainty in predicting efficacy based on MATS estimated coverage due to heterogeneity of antibody responses and waning of antigen-specific titres over time
- an unacceptably high ICER that was based on uncertain assumptions about the extent and duration of effect and herd immunity

A minor re-submission was sought in July 2015 that presented a cost-utility model with a revised base case resulting in cost per QALY outcomes ranging from of AU$45,000–AU$200,000 per QALY for the vaccination schedules compared to no vaccination, a ‘preferred strategy yielding a cost-effectiveness range between AU$105,000 and AU$200,000 (i.e., approximately 5 to 10 QALYs per $m).

Attachments

PHARMAC
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SUBCOMMITTEE MEMORANDUM

To: Immunisation Subcommittee

From: Therapeutic Group manager

Date: February 2019

Meningococcal B vaccine (Bexsero) for the prevention of invasive meningococcal group B disease

SUMMARY OF PHARMACEUTICAL			
Brand Name	Bexsero	**Chemical Name**	Multicomponent meningococcal group B vaccine (recombinant, adsorbed) (4CMenB)
Indications	Immunisation against invasive disease caused by N. meningitidis group B strains in infants	**Presentation**	0.5 mL suspension for injection in a prefilled syringe
Therapeutic Group	National Immunisation Schedule	**Dosage**	2+1 dosing schedule with primary doses at 6 weeks and 3 months of age and a booster dose at 12 months
Supplier	GlaxoSmithKline New Zealand Limited	**Application Date**	January 2018
MOH Restrictions	Prescription medicine	**Proposal type**	New listing
Current Subsidy	NA	**Proposed Restriction**	Universal infant vaccination
Proposed Subsidy	s9(2)(b) per dose	**Manufacturer's Surcharge**	Nil

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QUESTIONS TO SUBCOMMITTEE

Note to Subcommittee members: These questions have been identified by PHARMAC staff as being particularly relevant to the application. Please feel free to provide additional information as appropriate.

Need

1. What is the Subcommittee's view of the patient number estimates by the applicant and PHARMAC staff?
2. Does meningococcal group B disease disproportionally affect:
    - Māori?
    - Pacific people?
    - Other groups already experiencing health disparities relative to the wider New Zealand population (eg. NZ Dep 9-10 deprivation, refugees/asylum seekers)?

Health benefit

3. Which patient population would benefit most from 4CMenB (Bexsero)?
4. What is the strength and quality of evidence, including its relevance to NZ, for health benefits that may be gained from 4CMenB (Bexsero)?
5. Should 4CMenC (Bexsero) be funded, are there any consequences to the health system that have not been noted in the application?

Suitability

6. Are there any non-clinical features of 4CMenB (Bexsero) that may impact on use, either by the patient, by family, or by healthcare workers, that have not been considered in the application?

Costs and savings

7. What are the health care resource utilisation implications associated with key meningococcal B sequelae, including physical, neurological, psychological and behavioural sequelae?
8. Are the uptake assumptions of 25% reasonable for high risk group entrants and high risk groups catch up programme?

Recommendations

9. Should Bexsero be listed in the Pharmaceutical Schedule for universal childhood immunisation with a 2+1 dosing schedule?
    9.1. Name the Factors for Consideration particularly relevant to a positive or negative recommendation and explain why each is relevant.
10. If listing for universal childhood vaccination is recommended, what priority rating would you give to this proposal? **[low / medium / high / only if cost-neutral]**?
11. Are there any special groups outside the childhood immunisation schedule that should be included in the access criteria, such as high risk groups, close contacts or people in close living circumstances?

12. Should Bexsero be listed in the Pharmaceutical Schedule for high risk groups and close contacts?

    12.1. How should the high risk groups be defined?

13. If listing is recommended for high risk groups and close contacts, what priority rating would you give to this proposal? **[low / medium / high / only if cost-neutral]**?

14. Should Bexsero be listed in the Pharmaceutical Schedule for people in close living circumstances?

    14.1. How should close living circumstances be defined?

15. If listing is recommended for close living circumstances, what priority rating would you give to this proposal? **[low / medium / high / only if cost-neutral]**?

16. Does the Subcommittee have any recommendations additional to the application?

PURPOSE OF THIS PAPER

The purpose of this paper is to seek advice from the Subcommittee regarding the funding of meningococcal B (Men B) vaccine for universal childhood vaccination of infants on the National Immunisation Schedule, to inform the evaluation of the 2018/19 Vaccines Request for Proposals (RFP).

DISCUSSION

BACKGROUND

Previous consideration of prevention of meningococcal group B disease

At its February 2015 meeting, the Subcommittee noted that Men B had a higher incidence that meningococcal C (Men C) and recommended that PHARMAC should assess the epidemiology of the incidence in New Zealand for similarities with patterns in the UK and Australia.

Previous consideration of meningococcal B vaccines

. In February 2018, at the recommendation of the Ministry of Health Communicable Diseases Team, PHARMAC purchased 100 doses of Bexsero as emergency stock that could be used in the event of a meningococcal B outbreak in a multi-occupancy residential setting such as university halls of residence.

The Immunisation Subcommittee of PTAC reviewed an application for 4CMenB (Bexsero) at its meeting in April 2018 and recommended that 4CMenB be funded for universal infant vaccination as part of the Infant Immunisation Schedule, with a 2+1 dosing schedule, with a medium priority. The Subcommittee also recommended that 4CMenB be funded with a medium priority for high risk groups and close contacts, based on high clinical need.

The relevant minutes of the April 2018 Subcommittee minutes are attached in Appendix 1.

PTAC will review the supplier application for 4CMenB (Bexsero) at its meeting in February 2019. The minutes from the February 2019 PTAC meeting will not be available for the Subcommittee meeting, but PHARMAC staff will provide an update to the Subcommittee at this meeting.

Vaccines RFP underway

PHARMAC issued an RFP for various vaccines in November 2018, including a request for proposals for a meningococcal B vaccine. The RFP closed on 18 January 2019, with implementation of all changes from the RFP, other than influenza vaccines, planned for July 2020. s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j)

s9(2)(b)(ii), s9(2)(ba)(i) and

Need

Description of the disease

Invasive meningococcal disease (IMD) is a rapid, often fatal disease, that can have devastating lifelong consequences for survivors and their whānau. Approximately 10% of patients die even with appropriate medical care and up to 20% of survivors have major permanent sequalae including brain damage, adrenal impairment, hearing loss, renal failure and disfigurement. It is easily misdiagnosed, progressing from non-specific symptoms, such as fever and irritability, to death within 24 hours of onset, even with medical intervention. This rapid progression leaves clinicians with a narrow window for diagnosis and intervention, underscoring the need for disease prevention through immunisation.

Epidemiology

In New Zealand, IMD rates are higher than comparable countries such as Australia, U.S., Canada and England. Meningococcal Group B causes most cases of meningococcal disease in New Zealand (57.4% (523/911) over the period 2007–2016). In 2016, 70% of meningococcal cases that could be typed were serogroup B, and in the less than 5-year age group the proportion is higher at 82%. In 2017, 68 out 112 (60%) of notified meningococcal cases were serogroup B.

Updated epidemiology for meningococcal disease cases in New Zealand from 2013 to 2018 is provided in Table 1 below, and group incidence by age group for 2017 and 2018 is provided in Table 2 below.

Table 1. Meningococcal disease cases by group by year, 2013-2018

Strain group	Year						
	2013	2014	2015	2016	2017	2018	2019**
Group B	**30**	**26**	**41**	**47**	**70**	**51**	**2**
B:P1.7-2,4	11	13	10	23	27	16	1
Other group Bs	19	13	31	24	43	35	1
Group C	**17**	**6**	**6**	**8**	**11**	**10**	**2**
C:P1.5-1,10-8	15	5	3	4	8	6	2
Other group Cs	2	1	3	4	3	4	0
Other	**11**	**4**	**12**	**12**	**24**	**52**	**0**
Group W	5	0	6	5	12	33	0
Group Y	4	3	6	7	11	16	0
Group E	0	1	0	0	0	0	0
Group X	0	0	0	0	0	1	0
Non-groupable	2	0	0	0	1	2	0

*2017-2019 data as of 15 Jan 2019
**2019 data from 1-15 Jan 2019 only
Source: ESR

Table 2. Number of meningococcal disease cases by strain group 2017 and 2018

2017

Strain group	Age group						Total
	<1	1 to 4	5 to 9	10 to 14	15 to 19	20+	
Group B	**12**	**17**	**4**	**1**	**10**	**26**	**70**
B:P1.7-2,4	2	4	1	0	6	14	27
Other group Bs	10	13	3	1	4	12	43
Group C	**1**	**2**	**1**	**0**	**4**	**3**	**11**
C:P1.5-1,10-8	1	0	1	0	4	2	8
Other group Cs	0	2	0	0	0	1	3
Other	**1**	**2**	**0**	**2**	**1**	**18**	**24**
Group W	1	0	0	1	1	9	12
Group Y	0	2	0	1	0	8	11
Non-groupable	0	0	0	0	0	1	1

2018

Strain group	Age group						Total
	<1	1 to 4	5 to 9	10 to 14	15 to 19	20+	
Group B	**11**	**7**	**3**	**3**	**12**	**15**	**51**
B:P1.7-2,4	1	1	0	0	5	9	16
Other group Bs	10	6	3	3	7	6	35
Group C	**1**	**1**	**0**	**1**	**2**	**5**	**10**
C:P1.5-1,10-8	1	1	0	0	1	3	6
Other group Cs	0	0	0	1	1	2	4
Other	**4**	**5**	**5**	**1**	**4**	**33**	**52**
Group W	3	4	3	1	3	19	33
Group Y	1	1	1	0	0	13	16
Group X	0	0	0	0	0	1	1
Non-groupable	0	0	1	0	1	0	2

Meningococcal B Epidemic in New Zealand

From 1991 – 2007 New Zealand experienced a prolonged epidemic of meningococcal B, driven by a single group B subtype (B: P1.7-2,4), resulting in 6,128 cases and 252 deaths. The MeNZB vaccine was introduced from 2004 – 2008 to manage the epidemic and the number of disease notifications declined dramatically. The immune response to the vaccine was short-lived and it is not expected that anyone previously vaccinated would still have existing immunity to B disease.

The health need of the person

Survivors of IMD face a significant burden due to long-term physical, neurological and psychological sequelae which differ considerably in type, severity, duration and associated cost. IMD is a rapidly progressing and often fatal disease with death occurring in approximately

10% of patients. IMD is associated with significant morbidity with up to 20% of survivors of IMD experiencing permanent sequelae including brain damage, adrenal impairment, hearing loss, renal failure and disfigurement. More than one third of survivors of childhood meningococcal B disease experience lifelong deficits such as psychological disorders, digit amputations, minor or unilateral hearing loss and minor communication deficits.

The availability and suitability of existing medicines, medical devices and treatments

There is currently no vaccine on the National Immunisation Schedule for the prevention of meningococcal group B disease.

The health need of family, whānau, and wider society

PHARMAC acknowledge that there may be a health need for other people as a result for caring for patients with IMD.

IMD is associated with significant mortality and morbidity and poses a significant burden on families and whānau. Long-term sequelae associated with IMD requires care from family and whānau members. This imposes a high burden associated with travel to from appointments, providing care and the potential need to cater to special needs by altering the home environment. Parents of children with severe IMD report experiencing psychological distress for months/years due to impact of the disease on the child and guilt associated with not recognizing the symptoms of the disease (Ehrlich et al., Pediatr Rehabil; 2005:220-4). There is a large emotional toll on the family or whānau as they cope with the loss of a family member due to IMD.

Due to the non-specific symptoms and rapid progression, IMD is often misdiagnosed which can also lead to considerable stress for healthcare workers.

The impact on Pacific health areas of focus and Pacific health outcomes

Invasive meningococcal disease disproportionately affects those of Māori and Pacific descent with these populations exhibiting four times higher rates of meningococcal B disease across all age groups compared to the non-Māori/non-Pacific population from 2007–2016 children. Māori and Pacific infants <1 year of age had a six times higher rate of meningococcal B disease from 2007–2016 compared to non-Māori/non-Pacific Island children. The disproportionate distribution of IMD among Māori may be attributed to their low socioeconomic status and household crowding.

Health Benefit

Details of the pharmaceutical under consideration

New Zealand Regulatory Approval

Bexsero was approved for use in New Zealand by Medsafe in July 2018 for the following indications:

- for active immunisation against invasive disease caused by N. meningitidis group B strains; and

- for vaccination of individuals from 2 months of age and older.

Recommended Dosage and Treatment Paradigm

s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j) for a 2+1 dosing schedule. The primary administrations would be at 6 weeks and 3 months, and a booster at 12 months.

With a 2+1 dosing schedule, the primary doses are aligned with the current National Immunisation Schedule (NIS), but the 12-month booster would be an additional visit which would result in additional work for vaccinators and increased vaccination claim costs for the Ministry of Health. The booster vaccination could be given at 15 months to align with the NIS, but this would mean five injections would be given at the 15 months visit under the current schedule.

At its April 2018 meeting, the Immunisation Subcommittee recommended a 2+1 dosing schedule. Members noted that adding 4CMenB to the infant schedule would necessitate an additional immunisation visit at 12 months and changes to the infant schedule to ensure optimal vaccine combinations at each visit.

International Recommendations

Table 3: International recommendations regarding the funding of 4CMenB

Country	Vaccine	Programme
Australia	Bexsero	A state-wide meningococcal B immunisation programme for babies, as well as a catch up programme has been funded in South Australia since October 2018. An adolescent school-based immunisation programme will commence in February 2019, as well as a catch-up programme for those aged 17-20 years of age.
Canada	Bexsero	Meningococcal B vaccination has been funded since December 2014 for children at high risk of developing IMD.
England and Scotland	Bexsero	Meningococcal B vaccination has been part of the NHS routine childhood vaccination programme since September 2015.

Literature Search

PHARMAC staff conducted a PubMed search (search terms: 4CMenB) and identified the following additional publications regarding meningococcal B vaccination that were not identified in the 2018 supplier application previously considered by the Subcommittee.

- De Serres et al. Short-term safety of 4CMenB vaccine during a mass meningococcal B vaccination campaign in Quebec, Canada. Vaccine; 2018:8039-46
- Macias Parra et al. Immunogenicity and safety of the 4CMenB and MenACWY-CRM meningococcal vaccines administered concomitantly in infants: A phase 3b, randomized controlled trial. Vaccine; 2018:7609-17.
- Biolchi et al. Evaluation of strain coverage of the multicomponent meningococcal serogroup B vaccine (4CMenB) administered in infants according to different immunisation schedules. Hum Vaccin Immunother; 2018. doi: 10.1080/21645515.2018.1537756

- Bryan P et al. Safety of multicomponent meningococcal group B vaccine (4CMenB) in routine infant immunisation in the UK: a prospective surveillance study. Lancet Child Adolesc Health; 2018:395-403.
- Olbrich KJ et al. Systematic Review of Invasive Meningococcal Disease: Sequelae and Quality of Life Impact on Patients and Their Caregivers. Infect Dis Ther: 2008:421-438.

Consequences for the health system

Dosing schedule

s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j) proposed a 2+1 dosing schedule. The dosing schedule has the primary administrations at 6 weeks and 3 months, and a booster at 12 months. With this dosing schedule, the primary doses are aligned with the current NIS, but the 12-month booster would be an additional visit which would result in additional work for vaccinators and increased vaccination claim costs for the Ministry of Health. The booster vaccination could be given at 15 months to align with the NIS, but this would mean five injections would be given at the 15 months visit under the current schedule.

Paracetamol administration

The supplier recommends prophylactic administration of paracetamol with every dose of 4CMenB to manage the known reactogenicity of the vaccine followed by two more doses 6 hours apart. Paracetamol is currently not recommended to be administered for childhood vaccinations, so this would represent an additional cost and increase in vaccinator workload to manage this. Vaccinators would need to be provided with training around the recommendation for prophylactic paracetamol.

Suitability

The features of the medicine or medical device that impact on use

Pre-filled syringes

Bexsero is supplied as a 0.5 mL suspension in a pre-filled syringe (Type I glass) with a plunger stopper (Type I bromobutyl rubber) and with a protective tip cap (Type II rubber). Available pack sizes are one syringe with or without needles, or ten syringes without needles. Not all pack sizes may be distributed in New Zealand.

One dose (0.5 mL) contains:

Recombinant *Neisseria meningitidis* group B fHbp fusion protein	50 mcg
Recombinant *Neisseria meningitidis* group B NadA protein	50 mcg
Recombinant *Neisseria meningitidis* group B NHBA fusion protein	50 mcg
OMV from *Neisseria meningitidis* group B strain NZ98/254 measured as amount of total protein containing the Porin A (PorA P1.4)	25 mcg

Costs and Savings

Health-related costs and savings to the person, their family, whānau and wider society

Bexsero is currently available for private purchase. Although data on current private purchases of Bexsero has not been found, PHARMAC staff anticipate current uptake of such vaccines to be low although recent publicity surrounding meningococcal disease would be likely to increase private sales.

Administration of vaccine typically requires GP consultation, vaccination purchase and administration (e.g. nurse). Should any sub-populations or all the relevant populations be provided access through the National Immunisation Schedule (NIS), they would incur no vaccination dose or administration costs should their administration coincide with the existing visits of the NIS.

With the 2+1 dosing schedule for infants, the primary doses are aligned with the current NIS, but the 'at 12-months' booster would be an additional visit which would result in additional work for vaccinators and increased vaccination claim costs for the Ministry of Health. The booster vaccination could be given at 15 months to align with the NIS, but this would mean five injections would be given at the 15 months visit under the current schedule.

The base case analysis here assumes an additional vaccine administration cost for the booster dose. It is anticipated any 'at 12-months' booster would be part of a re-structuring of the timelines of the NIS and so administration cost must be accounted for.

Similarly, for the catch-up dosing of high-risk individuals (people in close living situations such as prisons, barracks, university halls of residence, and those boarding at boarding schools), additional vaccine administration costs are dependent on timing with respect to the NIS. For the purposes of budget impact assessment, it is assumed the dose is not aligned with the NIS and thus incurs administration costs.

Costs and savings to pharmaceutical expenditure

The analysis presented below focuses on distinct population considerations reflecting vaccination population scenarios proposed for funding by the Immunisation Subcommittee following the Vaccines RFP released in November 2018 and takes into account the pricing of the 4CMenB vaccine received in the RFP:

a) A universal '2 + 1' vaccination for infants. The 2+1 dosing schedule has the primary administrations at 3 weeks and 5 months and a booster at 12 months.

b) High-risk individuals (e.g. people in close living situations such as prisons, barracks, university halls of residence, and those boarding at boarding schools). Patients in the defined sub-populations are all older than 12 months. For analysis purposes it is assumed they would have two doses.

It should be noted consideration of the universal infant vaccination includes options where dosing for these high-risk individuals may be included in the overall proposal. If they were,

they would adopt the unit price of the given proposal. s9(2)(b)(ii), s9(2)(ba)(i) and PHARMAC is considering pricing proposals as follows for Bexsero 4CMenB (**Table 4**).

***Please note that all vaccine price information is <u>confidential</u> and not to be shared outside the Subcommittee. ***

Table 4 Proposed Vaccination Schedules and Pricing s9(2)(b)(ii), s9(2)(ba)(i) and

Vaccination schedule	Price per dose
High risk individuals only (e.g. people in close living situations such as prisons, barracks, university halls of residence, and those boarding at boarding schools)	s9(2)(b)
2+1 dosing schedule for universal vaccination +/- catch up (proposal 1 – s9(2)(b)(ii),	s9(2)(b)
2+1 dosing schedule for universal vaccination +/- catch up (proposal 2 – s9(2)(b)(ii), s9(2)(ba)(i)	s9(2)(b)

Source: PHARMAC (**<u>confidential</u>**).

Estimated Patient Populations

For infants (0 to 12 months), the estimated population is approximately 61,000. This figure may vary annually based on the changing birth rate, however it reflects a reasonable average yearly estimate. (Source: Stats NZ, August 2018 (http://archive.stats.govt.nz/infoshare/ViewTable.aspx?pxID=1f01ca00-da2d-4805-a7ea-96a0388966e2).

High-risk individuals in close-living sub-populations requested to be looked at by the Immunisation Subcommittee in May 2018 included people in close living situations such as prisons, barracks, university halls of residence, and those boarding at boarding schools (coverage primarily of those 13 to 19).

<u>Closed-Living Populations</u>

The following population data was presented to the Immunisation Subcommittee in August 2018 and deemed reflective of the patient populations previously requested to be considered by the Subcommittee. Data from the New Zealand Ministry of Education website "Education Counts" (www.educationcounts.gov.nz) estimates 174,000 students enrolled at Universities during 2016; enrolments have fluctuated in the last decade but overall remain at the same level as 2008. Considering technology institutes and other tertiary providers, there was an estimated 416,000 tertiary students (FTE) in New Zealand in 2016. Of these, it is estimated based on Education Counts information, these providers have 16,000 residential students in close living quarters, although this number could be higher.

Further, there are approximately 294,000 students enrolled in schools as at 1 July 2017 between the ages of 13 and 19 (only 1,765 aged 19). According to Education Counts, as of August 2018, there are 96 boarding schools in New Zealand, with an estimated aggregate boarding school population of 13,440. For reference, Education Counts estimated approximately 10,000 boarding school students in 2002.

Focusing on the specified closed-living sub-populations requested by the Immunisation Subcommittee in May 2018, it is assumed there are approximately 8,700 'new entrants' into the defined sub-populations annually and approximately 46,000 in total in these sub-populations (with 37,500 therefore deemed 'catch up' in any given year).

The table below summarises these estimates. It is assumed that the prison population continues to grow and thus new entrants to the system are incremental. For the armed forces, it is assumed new entrants are aged 18 to 19 and replace older members. These ages and the concept of 'replacement' is also assumed for new entrants in the university and boarding school populations.

Table 5 Estimated Relevant Sub-Populations

Patient Sub-population	Total (new annual)	Total (catchup)
Prisoners (sentenced)	74	7,409
Armed forces (barracks/quarters)	921	8,287
Tertiary education residential students (dormitories, residential living blocks)	5,000	11,000
Boarding school students (dormitories)	2,700	10,800
Total	**8,695**	**37,496**

Sources: New Zealand Defence Force (/www.nzdf.mil.nz/downloads/pdf/public-docs/2017/2016-2017-nzdf-annual-report.pdf); New Zealand Department of Corrections (Department of Corrections New Zealand, 2017 (http://www.corrections.govt.nz/resources/research_and_statistics/quarterly_prison_statistics.html); Education Counts (NZ Ministry of Health, www.educationcounts.govt.nz/statistics/tertiary-education/participation, www.educationcounts.govt.nz/statistics/schooling/student-numbers/6028, www.educationcounts.govt.nz/find-school).

Notes: Estimated boarding/close-living populations sourced from going to websites of the individual education providers listed in data tables provided by 'Education Counts'. Some listed boarding schools at 'Education Counts' did not specify boarding student population numbers; imputed values have been used based on average numbers of boarding schools with specified boarding populations (approximately 65% of the 96 listed schools had boarding student numbers published). Tertiary education residential student numbers are based on publicly available information referencing listed tertiary education providers from 'Education Counts', but may be higher.

Cost per patient

Vaccination costs

s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j)
s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j)
s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j) Cost per patient consists of both initial dose(s) and booster dose(s) as appropriate:

a) A universal 2+1 vaccination for infants. The 2+1 dosing schedule has the primary administrations at 6 weeks and 3 months and a booster at 12 months. By proposal:

   i) Proposal 1: s9(2)(b)(ii), (i.e., 3 × s9(2) per dose). Should high risk individuals be incorporated into this proposal they would cost s9(2)(b) (i.e., 1 × s9(2) per dose).

   ii) Proposal 2: s9(2)(b)(ii), (i.e., 3 × s9(2) per dose). Should high risk individuals be incorporated into this proposal they would cost s9(2)(b)(ii), (i.e., 1 × s9(2) per dose).

b) High-risk closed living individuals only, (e.g. sub-populations requested to be looked at by the Immunisation Subcommittee (people in close living situations such as prisons, barracks, university halls of residence, and those boarding at boarding schools) – coverage primarily of those 13 to 19)). As a stand-alone proposal, they would cost s9(2)(b)(ii), (i.e., 2 × s9(2) per dose).

***Please note that all vaccine price information is confidential and not to be shared outside the Committee. ***

Vaccine Administration Costs

Administration of the base vaccinations for infants is assumed to coincide with the NIS, therefore no additional administration costs are assumed. Administration of the booster dose for infants assumes an administration cost of $20 (reflecting its administration along with other NIS vaccinations as part of creation of an additional timepoint on the NIS at 12 months) and for high risk individuals a cost of $20 per dose.

Estimated Incremental Total Cost of Listing

Combined Pharmaceutical Budget (CPB) and total District Health Board (DHB) cost impact over the first five years of implementing the vaccination program has been estimated for the populations and proposals defined above. Note the NPV totals reflect discounting at 8% per annum.

It should be noted that vaccination is expected to reduce the number of patients experiencing acute and long-term consequences of infection and thus associated health care resource utilisation. Initial analysis by PHARMAC staff indicates that although this an important outcome of any vaccination program, that relative to vaccination program costs, this offset is anticipated to be relatively small in comparison. Should PHARMAC proceed with listing, PHARMAC staff will undertake more detailed analysis of health care resource cost impacts. We seek Subcommittee comment on health care resource utilisation associated with key meningococcal B sequelae, including physical, neurological, psychological and behavioural sequelae (amputation, blindness, hearing (including deafness), anxiety, facial scarring, severe neurological impairment etc.).

For the purposes of analysis by PHARMAC staff, uptake reflects feedback from the Immunisation Subcommittee in May 2018 on the specified sub-populations:

- 20% to 30% in closed living situations for adolescents (i.e. aged 13 to 19 in university residence, prisons and boarding schools); and
- 90% (for all doses) for infants (i.e., < 12 months). NIS full coverage targets for infants/children are typically 95%, but data from Ministry of Health as at March 2018 shows this has not quite been achieved (12-month completion is estimated at 93.6%, 24-months at 92%). This is also the assumption used by the supplier in their 2018 submission to PHARMAC.

For ease of comparison, **Table 10** summarises final estimated incremental costs of listing for all proposals for all populations, reflecting inclusion/exclusion of High-Risk Closed Living Sub-Populations.

High Risk Individuals

Table summarises the estimated annual CPB and DHB budget impacts of vaccination of high-risk individuals 'entering' this cohort (i.e., at age 13). Note the assumed price for this group separately is s9(2)(b) per vaccination. Administration costs are assumed. Over five years, the estimated NPV DHB impact would be approximately s9(2) (s9(2)(b) CPB). Note that should this population be bundled into Proposal 2, it would assume a per dose cost of s9(2)(b). Over five years, the estimated NPV DHB impact would be approximately s9(2)(b) (s9(2)(b) CPB).

Table 6 Estimated CPB and DHB impact of immunising 'high risk' patients as a separate population group – entrants only

Item	Year 1	Year 2	Year 3	Year 4	Year 5
Patients (25% uptake)	2,174	2,174	2,174	2,174	2,174
Vaccination Costs					
First dose	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)(ii),
Second dose	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)
Booster (2nd year)					
Total CPB impact	s9(2)(b)	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)	s9(2)(b)(ii),
Administration Costs					
First/Second/Booster dose	$86,960	$86,960	$86,960	$86,960	$86,960
Total DHB impact	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)

Notes: Yearly amounts are undiscounted. Analysis assumes vaccine cost of approximately s9(2) Administration cost assumed.

Table summarises the estimated annual CPB and DHB budget impacts of vaccination of high-risk individuals 'entering' this cohort, including a 'catch-up' for all in the high-risk population cohort. Note the assumed price for this group separately is s9(2)(b) per vaccination. Administration costs are assumed. Over five years, the estimated NPV DHB impact would be approximately s9(2)(b) (s9(2)(b) CPB). Note that should this population be bundled into Proposal 2, it would assume a per dose cost of s9(2)(b). Over five years, the estimated NPV DHB impact would be approximately s9(2)(b) (s9(2)(b) CPB).

Table 7 Estimated CPB and DHB impact of immunising 'high risk' patients as a separate population group – entrants and 'catch-up' in the first year

Item	Year 1	Year 2	Year 3	Year 4	Year 5
Patients (25% uptake)	11,548	2,174	2,174	2,174	2,174
Vaccination Costs					
First dose	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)
Second dose	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)(ii),
Booster (2nd year)					
Total CPB impact	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)	s9(2)(b)(ii),
Administration Costs					
First/Second/Booster dose	$431,920	$86,960	$86,960	$86,960	$86,960
Total DHB impact	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)

Notes: Yearly amounts are undiscounted. Analysis assumes vaccine cost of approximately s9(2) Administration cost assumed.

Table summarises the estimated annual CPB and DHB budget impacts of universal vaccination of infants under Proposal 1. Note the first two doses are assumed to incur no vaccine administration costs, but that the booster dose (in the following year) is assumed to. Over five years, the estimated NPV DHB impact would be approximately s9(2)(b) (s9(2)(b)(ii), CPB).

Table 8 Estimated CPB and DHB impact of immunising infants (0 to 12 months) under '2+1' Proposal 1

Item	Year 1	Year 2	Year 3	Year 4	Year 5
Patients (90% uptake)	54,000	54,000	54,000	54,000	54,000
Vaccination Costs					
First dose	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Second dose	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Booster (2nd year)		s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Total CPB impact	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Administration Costs					
First/Second/Booster dose		$1,080,000	$1,080,000	$1,080,000	$1,080,000
Total DHB impact	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),

Notes: Yearly amounts are undiscounted. Uptake reflects estimate provided by Immunisation Sub-committee in May 2018 for infants. Analysis assumes vaccine cost of approximately s9(2) per dose. No administration costs for the first two doses are assumed based on scheduling being in line with the New Zealand NIS; it is assumed the booster dose incurs an administration cost ($20) reflecting the creation of a new time point on the NIS. The cost of the booster dose is incurred in the year following the initial two doses.

Universal Vaccination Program for Infants: Proposal 2

Table summarises the estimated yearly CPB and DHB budget impacts of universal vaccination of infants under Proposal 2. Note the first two doses are assumed to incur no vaccine administration costs, but that the booster dose (in the following year) is assumed to. Over five years, the estimated NPV DHB impact would be approximately s9(2)(b) (s9(2)(b) CPB).

Table 9 Estimated CPB and DHB impact of immunising infants (0 to 12 months) under '2+1' Proposal 2

Item	Year 1	Year 2	Year 3	Year 4	Year 5
Patients (90% uptake)	54,000	54,000	54,000	54,000	54,000
Vaccination Costs					
First dose	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Second dose	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Booster (2nd year)		s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Total CPB impact	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Administration Costs					
First/Second/Booster dose		$1,080,000	$1,080,000	$1,080,000	$1,080,000
Total DHB impact	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),

Notes: Yearly amounts are undiscounted. Uptake reflects estimated provided by Immunisation Sub-committee in May 2018 for infants. Analysis assumes vaccine cost of approximately s9(2) No administration costs for the first two doses are assumed based on scheduling being in line with the New Zealand NIS; it is assumed the booster dose incurs an administration cost ($20)

reflecting the creation of a new time point on the NIS. The cost of the booster dose is incurred in the year following the initial two doses.

Summary

For ease of comparison, **Table** summarises all proposals for all populations, reflecting inclusion/exclusion of High-Risk Closed Living Sub-Populations.

Table 10 Summary: Comparison of Total 5-year NPV CPB and DHB impact of funding Bexsero for defined populations

Vaccination schedule	Total Projected 5-year NPV CPB impact ($m)	Total Projected 5-year NPV DHB impact ($m)
High risk individuals only (entrants into high risk closed living adolescent population) s9(2) per dose	s9(2)	s9(2)(b)
High risk individuals only (entrants into high risk closed living adolescent population and 'catch up') - s9(2) per dose	s9(2)	s9(2)(b)
High risk individuals only (entrants into high risk closed living adolescent population) - s9(2) per dose	s9(2)	s9(2)(b)
High risk individuals only (entrants into high risk closed living adolescent population and 'catch up') - s9(2) per dose	s9(2)	s9(2)(b)
2+1 dosing schedule for universal vaccination without catch up for high risk individuals (proposal 1) s9(2) per dose	s9(2)(b)	s9(2)(b)
2+1 dosing schedule for universal vaccination with catch up for high risk individuals entering this cohort (proposal 1) - s9(2 per dose	s9(2)(b)	s9(2)(b)
2+1 dosing schedule for universal vaccination with catch up for high risk individuals entering this cohort and those already in the cohort (proposal 1) - s9(2 per dose	s9(2)(b)	s9(2)(b)
2+1 dosing schedule for universal vaccination without catch up for high risk individuals (proposal 2) s9(2) per dose	s9(2)(b)	s9(2)(b)
2+1 dosing schedule for universal vaccination with catch up for high risk individuals entering this cohort (proposal 2) - s9(2) per dose	s9(2)(b)	s9(2)(b)
2+1 dosing schedule for universal vaccination with catch up for high risk individuals entering this cohort and those already in the cohort (proposal 2) - s9(2) per dose	s9(2)(b)	s9(2)(b)

Note: Amounts are subject to rounding.

Cost Effectiveness (combining the Health Benefits and Costs quadrants)

The supplier submitted a cost-effectiveness assessment as part of their submission to PHARMAC in 2018. It uses a dynamic transmission model, which aims to model the number of vaccine preventable IMD cases with reference to the dynamic interaction between relevant patient population demographics, IMD epidemiology, carriage, population contact and the effect of the vaccine itself to determine likely preventable and prevented cases. Concurrently, the model overlays associated resource, cost and health consequences to determine ultimate incremental cost effectiveness.

In developing the model, the supplier undertook a systematic literature review to identify all economic evaluations of IMD and all relevant IMD serotypes including those specifically for the MenB vaccination. The model is in line with other health economic evaluations of a meningococcal B vaccine using dynamic transmission models. The model has been previously used by the supplier and accepted in many other countries including the UK and Australia and has been adapted for New Zealand for this analysis.

PHARMAC staff have reviewed the overall structure and deem it conceptually appropriate. However, the actual operational model presented as part of the submission is ultimately deemed unfit for PHARMAC's purposes. A thorough review of the model was undertaken by PHARMAC staff and numerous issues were noted. Ultimately, key issues that affect its viability in testing the ultimate cost-effectiveness claim are:

- While acknowledging the inevitable complexity of modelling infectious diseases, the model is of extremely large size and of great difficulty to navigate. While quite detailed in explaining its operation, presented in Microsoft Office Excel software, it takes significant time to operate.
- The model is ultimately a 'black box', i.e., it uses hard coded 'behind the scenes' programming instructions to turn model inputs into final results. This means that while inputs and final outputs are visible, the user is unable to trace in between how inputs are 'converted' by the model into final results.

This model therefore does not readily adhere to the guidance of PHARMAC's *Prescription for Pharmacoeconomic Analysis (PFPA) Methods for Cost-Utility Analysis* (i.e., "Models should avoid unnecessary complexity and should be transparent, well described and reproducible").

On the other hand, the suppliers' own estimate of cost-effectiveness s9(2)(b)(ii), The supplier submission estimates the cost per quality adjusted life year (QALY) of the infant '2+1' program at between s9(2)(b)(ii), (for a 2+1 program) and s9(2)(b)(ii), (3+1) (or s9(2) to s9(2) QALYs per $1m). The effective price of 4CMenB originally proposed was s9(2)(b) per dose. Therefore, the total vaccine cost for a 3+1 4CMenB vaccination schedule was s9(2)(b)(ii), per infant as the base case. The total cost for a 2+1 4CMenB vaccination schedule base case was s9(2)(b)(ii), per infant.

PHARMAC staff, testing this result by using the model (assuming for this purpose it is relatively valid in translating inputs into final results), including by careful review of input values and assumptions, believe the likely true value of the base case (i.e., excluding any cross-protection benefit afforded for Meningococcal W) to be closer to s to s QALYs per $m. This is based on a per dose price of s9(2)(b) as per the RFP. It should be noted that the design of the model

does not provide for estimating the cost-effectiveness of 'high-risk individuals' (defined as per this paper).

Results are sensitive to varying degrees to assumptions regarding dose cost, incidence (including the proportion of meningococcal cases that are serogroup B), the case fatality ratio (CFR), sequelae incidence and costs, assumptions about quality of life impact, demographic case distribution, inclusion of cross-protection for meningococcal W and discounting. Assuming a combination of highly favourable assumptions, PHARMAC staff estimate cost-effectiveness may at best reach between s to s QALYs per $m (i.e., s9(2)(b)(ii), to s9(2)(b)(ii), per QALY). It should be noted that should per dose price be reduced s9(2) (i.e., to s9(2)(b)), cost-effectiveness would be approximately s9(2)(b)(ii), per QALY or s9(QALYs per $1m.

PHARMAC staff have compared this result with results reported in published literature and as evaluated by other international agencies. Studies quoted in the supplier submission note QALYs per $m estimates ranging from 1.2 (Lecocq et al 2016) to 3.2 (Christensen et al 2014) for a '2+1' infant scheme.

PHARMAC staff have also considered the commentary of the UK's Joint Committee on Vaccination and Immunisation (JCVI) in 2014, particularly its conclusions regarding its deliberations on the cost-effectiveness of using serogroup B meningococcal (MenB) vaccine in the UK, both routinely in infants and in at-risk groups. The JCVI makes its decisions on vaccines separately from the National Institute for Health and Care Excellence (NICE), which looks at other medicines, and operates a slightly different health economic rating. Its current cost-effectiveness threshold is set at £20,000 per QALY. It is also noted that in comparison, NICE has a general cost per QALY threshold for acceptability of decisions of approximately £30,000 per QALY.

Following iterations of analysis performed independently, based on specific JCVI feedback, it concluded, "*The consensus of the Committee was that whilst uncertainty remained, and whilst in some scenarios the vaccine would not be cost-effective at a positive vaccine price, the results of the final iteration of the cost-effectiveness model indicated that for an infant programme, in the scenarios considered most plausible by the Committee, the vaccine was still cost effective (at a very low positive price)*."

The JCVI did not publicly disclose what such a price would be deemed 'cost-effective'. It should be noted that final analysis incorporated revisions suggested by the JCVI including:

- Inclusion in the base case model of a quality of life adjustment factor (QAF) of 3 agreed by the JCVI in June 2013 (as opposed to this being accounted for in an additional sensitivity analysis as had been done previously);
- Inclusion of a proportion of litigation costs associated with meningococcal disease in the NHS; and
- Inclusion of quality of life losses to family members.

It should be noted that none of these economic evaluation practices are in accordance with the recommendations of PHARMACs PFPA for base case economic evaluation. PHARMAC staff in particular tested the impact of using a QAF in the supplier model and noted that by itself it considerably improved the cost-effectiveness of final outcomes.

Finally, PHARMAC staff considered the feedback of the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, which has previously considered Bexsero. In November 2013, a major submission requested the inclusion of 4CMenB in the Australian National Immunisation Program (NIP) with a proposed vaccination schedule of 3+1 in infants, a two-dose course in adolescents and a catch-up programme in older infants, toddlers and adolescents. The submission presented an incremental cost per QALY between AU$45,000 and AU$75,000 per QALY (i.e., 13 to 22 QALYs per $1m). The PBAC expressed several concerns including:

- lack of direct evidence of vaccine efficacy against infection and disease
- lack of evidence demonstrating ability of vaccine to generate a population level protective herd immune response
- increasing uncertainty in predicting efficacy based on MATS estimated coverage due to heterogeneity of antibody responses and waning of antigen-specific titres over time
- an unacceptably high ICER that was based on uncertain assumptions about the extent and duration of effect and herd immunity

A minor re-submission was sought in July 2015 that presented a cost-utility model with a revised base case resulting in cost per QALY outcomes ranging from of AU$45,000–AU$200,000 per QALY for the vaccination schedules compared to no vaccination, a 'preferred strategy' (not explicitly identified in the released Public Summary Document) yielding a cost-effectiveness range between AU$105,000 and AU$200,000 (i.e., approximately 5 to 10 QALYs per $m).

APPENDICES

Appendix 1: Christensen, H., et al., Re-evaluating cost effectiveness of universal meningitis vaccination (Bexsero) in England: Modelling study. BMJ (Online), 2014. 349 (no pagination)(g5725).

Appendix 2: Department of Health and Public Health England. Joint Committee on Vaccination and Immunisation. Minute of the meeting on Tuesday 11 and Wednesday 12 February 2014. 2014; Available from: https://app.box.com/s/iddfb4ppwkmtjusir2tc/1/2199012147/18992168807/1

Appendix 3: Lecocq, H., et al., Epidemiological impact and cost-effectiveness of introducing vaccination against serogroup B meningococcal disease in France. Vaccine, 2016. 34(19): p. 2240-50.

Appendix 4: Pharmaceutical Benefits Advisory Committee. Multicomponent Meningococcal Group B Vaccine, 0.5mL, injection, prefilled syringe, Bexsero® - November 2013. 2013; Available from: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/201311/meningococcal-vaccine. 98.

Appendix 5: Pharmaceutical Benefits Advisory Committee. Multicomponent meningococcal group b vaccine (4cmenb); 0.5 mL suspension for injection pre-filled syringe; Bexsero®. 2015; Available from:

http://www.pbs.gov.au/info/industry/listing/elements/pbacmeetings/psd/2015-07/mulit-component-meningococcal-group-b-vaccine-psd-july-2015.

THE FACTORS FOR CONSIDERATION

Factors are presented here in the order they appear in the paper, without implying any ranking or relative importance.

NEED

- The health need of the person
- The availability and suitability of existing medicines, medical devices and treatments
- The health need of family, whānau, and wider society
- The impact on the Māori health areas of focus and Māori health outcomes
- The impact on the health outcomes of population groups experiencing health disparities
- The impact on Government health priorities

HEALTH BENEFITS

- The health benefit to the person
- The health benefit to family, whānau and wider society
- Consequences for the health system

SUITABILITY

- The features of the medicine or medical device that impact on use by the person
- The features of the medicine or medical device that impact on use by family, whānau and wider society
- The features of the medicine or medical device that impact on use by the health workforce

COSTS AND SAVINGS

- Health-related costs and savings to the person
- Health-related costs and savings to the family, whānau and wider society
- Costs and savings to pharmaceutical expenditure
- Costs and savings to the rest of the health system

PHARMACEUTICAL SCHEDULE APPLICATION

To: PTAC

From: Therapeutic Group Manager, Vaccines

Date: February 2019

Meningococcal B vaccine (Bexsero) for the prevention of invasive meningococcal group B disease

SUMMARY OF PHARMACEUTICAL			
Brand Name	Bexsero	**Chemical Name**	Multicomponent meningococcal group B vaccine (recombinant, adsorbed) (4CMenB)
Indications	Immunisation against invasive disease caused by N. meningitidis group B strains in infants	**Presentation**	0.5 mL suspension for injection in a prefilled syringe
Therapeutic Group	National Immunisation Schedule	**Dosage**	3+1 dosing schedule with primary doses at 6 weeks, 3 and 5 months of age and a booster dose at 12 months OR 2+1 dosing schedule with primary doses at 6 weeks and 3 months of age and a booster dose at 12 months
Supplier	GlaxoSmithKline New Zealand Limited	**Application Date**	January 2018
MOH Restrictions	Prescription medicine	**Proposal type**	New listing
Current Subsidy	NA	**Proposed Restriction**	Universal infant vaccination
Proposed Subsidy	s9(2)(b) per dose (Proposed price may change following the vaccines RFP)	**Manufacturer's Surcharge**	Nil

QUESTIONS TO PTAC

Note to PTAC members: These questions have been identified by PHARMAC staff as being particularly relevant to the application. Please feel free to provide additional information as appropriate.

Need

1. What is the strength and quality of evidence in relation to health need due to invasive meningococcal disease?
2. Should the assessment of 4CMenB (Bexsero) include the possibility of a future epidemic, and if so, what is the likelihood of one occurring in the next ten years?
3. Should the assessment of 4CMenB (Bexsero) include the health need and potential health benefits arising from cross-strain protection?
4. Is it reasonable to apply the data for all strains of *N meningitidis* to Meningococcal Group B infections, and if not, which statistics would be different for the strains targeted by the 4CMenB (Bexsero) vaccine?

Health benefit

5. Which patient population would benefit most from 4CMenB (Bexsero)?
6. What is the strength and quality of evidence, including its relevance to NZ, for health benefits that may be gained from 4CMenB (Bexsero)?
7. Would 4CMenB (Bexsero) produce a health benefit for family, whānau or wider society, additional to the health benefits for people with invasive meningococcal B disease? If so how, and what is the strength and quality of evidence for this benefit?
8. Should 4CMenB (Bexsero) be funded, are there any consequences to the health system that have not been noted in the application?

Suitability

9. Are there any non-clinical features of 4CMenB (Bexsero) that may impact on use, either by the patient, by family, or by healthcare workers, that have not been considered in the application?

Costs and savings

Note to Committee: Further questions relating to costs and savings will be included in the late paper about meningococcal B costs.

General

10. Is there any data or information missing from the application, in particular clinical trial data and commentary?

Recommendations

11. Should Bexsero be listed in the Pharmaceutical Schedule for universal childhood immunisation?
    - Name the Factors for Consideration particularly relevant to a positive or negative recommendation and explain why each is relevant.
12. If listing is recommended, does the Committee recommend a 3+1 or 2+1 dosing schedule?
13. If listing for universal childhood vaccination is recommended, what priority rating would you give to this proposal? **[low / medium / high / only if cost-neutral]**?
14. Are there any special groups outside the childhood immunisation schedule that should be included in the access criteria, such as high risk groups or close contacts?
15. Should Bexsero be listed in the Pharmaceutical Schedule for high risk groups and close contacts?
16. If listing is recommended for high risk groups and close contacts, what priority rating would you give to this proposal? **[low / medium / high / only if cost-neutral]**?
17. Does the Subcommittee have any recommendations additional to the application?

PURPOSE OF THIS PAPER

The purpose of this paper is to seek advice from the Committee regarding an application from GSK for the use of a meningococcal B vaccine (Bexsero) for universal childhood vaccination on the National Immunisation Schedule for the prevention of invasive meningococcal group B disease.

DISCUSSION

BACKGROUND

Previous consideration of prevention of meningococcal group B disease

At its February 2015 meeting, the Immunisation Subcommittee noted that meningococcal B had a higher incidence that meningococcal C and recommended that PHARMAC should assess the epidemiology of the incidence in New Zealand for similarities with patterns in the UK and Australia.

Previous consideration of meningococcal B vaccines

This is the first supplier application for a meningococcal B vaccine for universal vaccination to be considered by the Subcommittee or PTAC. In February 2018, at the recommendation of the Ministry of Health Communicable Diseases Team, PHARMAC purchased 100 doses of Bexsero as emergency stock that could be used in the event of a meningococcal B outbreak in a multi-occupancy residential setting such as university halls of residence.

The Immunisation Subcommittee of PTAC reviewed an application for 4CMenB (Bexsero) at their meeting in April 2018 and recommended that 4CMenB be funded for universal infant vaccination as part of the Infant Immunisation Schedule, with a 2+1 dosing schedule, with a medium priority. The Subcommittee also recommended that 4CMenB be funded with a medium priority for high risk groups and close contacts, based on high clinical need.

The relevant minutes of the April 2018 Subcommittee minutes are attached in Appendix 1.

Vaccines RFP underway

PHARMAC issued an RFP for various vaccines in mid-December 2018, including a request for proposals for a meningococcal B vaccine. The deadline for proposals is 18 January 2019, with implementation of all changes from the RFP, other than influenza vaccines, planned for July 2020.

Need

Description of the disease

Invasive meningococcal disease (IMD) is a rapid, often fatal disease, that can have devastating lifelong consequences for survivors and their whānau. Approximately 10% of patients die even with appropriate medical care and up to 20% of survivors have major permanent sequalae including brain damage, adrenal impairment, hearing loss, renal failure and disfigurement. It is easily misdiagnosed, progressing from non-specific symptoms, such

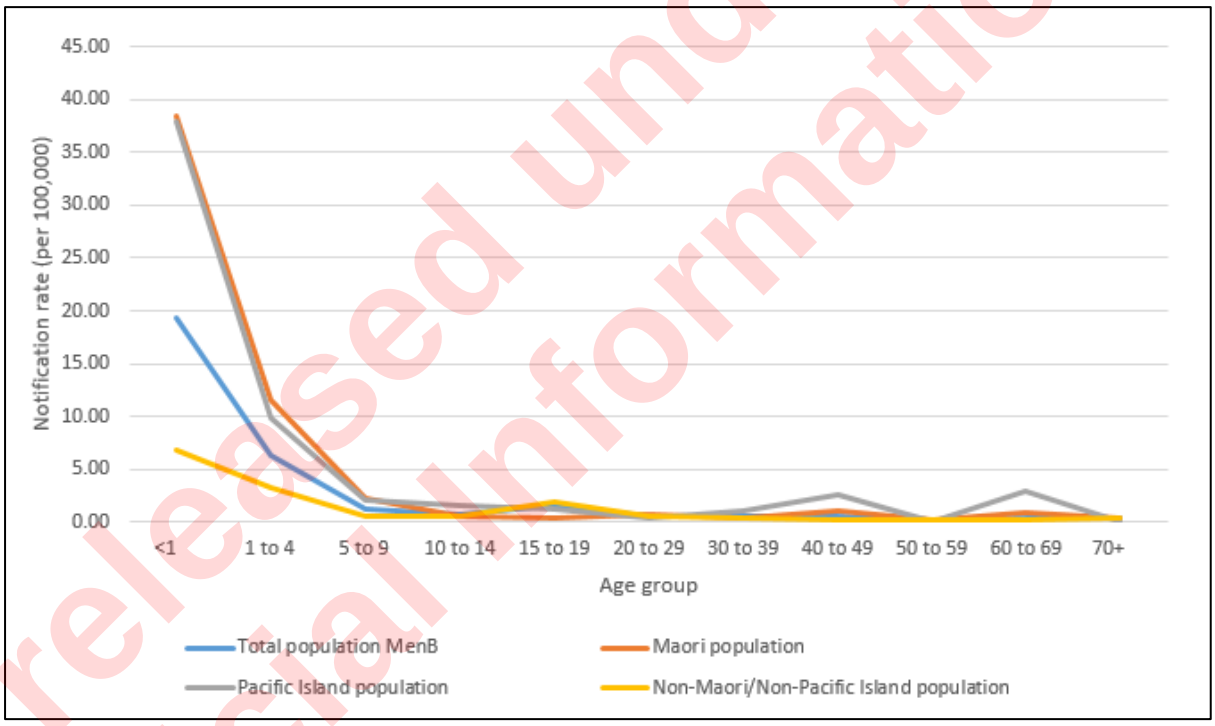
as fever and irritability, to death within 24 hours of onset, even with medical intervention. This rapid progression leaves clinicians with a narrow window for diagnosis and intervention, underscoring the need for disease prevention through immunisation.

Epidemiology

In New Zealand, IMD rates are higher than comparable countries such as Australia, U.S., Canada and England. Meningococcal Group B causes most cases of meningococcal disease in New Zealand (57.4% (523/911) over the period 2007–2016). In 2016, 70% of meningococcal cases that could be typed were serogroup B, and in the less than 5-year age group the proportion is higher at 82%. In 2017, 68 out 112 (60%) of notified meningococcal cases were serogroup B.

People of all ages and ethnicities are at risk of developing meningococcal B disease, although it disproportionately affects infants <1 year of age and Maori and Pacific Island populations (Figure 1).

Figure 1. Meningococcal B notification rate (per 100,000) stratified by age and ethnicity over 2007 – 2016



Source: ESR and Stats NZ; Supplier application attachment 01

Table 1. Meningococcal B notification rate (per 100,000) by age and ethnicity from 2014 – 2016

	Age	2014	2015	2016
Māori	<1	18.28	48.60	18.01
	1 to 4	8.98	4.54	3.05
	5 to 9	0.00	0.00	1.20
Pacific	<1	13.04	12.84	25.29
	1 to 4	3.26	6.42	9.48
	5 to 9	0.00	2.82	2.77
Total Population	<1	6.82	18.58	10.02
	1 to 4	4.40	4.87	4.49
	5 to 9	0.00	0.32	1.24

Source: ESR and Stats NZ; Supplier application attachment 01

Updated epidemiology for meningococcal disease cases in New Zealand from 2013 to 2018 is provided in Table 2 below, and group incidence by age group for 2017 and 2018 is provided in Table 3 below.

Table 2. Meningococcal disease cases by group by year, 2013-2018

Strain group	Year						
	2013	2014	2015	2016	2017	2018	2019**
Group B	**30**	**26**	**41**	**47**	**70**	**51**	**2**
B:P1.7-2,4	11	13	10	23	27	16	1
Other group Bs	19	13	31	24	43	35	1
Group C	**17**	**6**	**6**	**8**	**11**	**10**	**2**
C:P1.5-1,10-8	15	5	3	4	8	6	2
Other group Cs	2	1	3	4	3	4	0
Other	**11**	**4**	**12**	**12**	**24**	**52**	**0**
Group W	5	0	6	5	12	33	0
Group Y	4	3	6	7	11	16	0
Group E	0	1	0	0	0	0	0
Group X	0	0	0	0	0	1	0
Non-groupable	2	0	0	0	1	2	0

*2017-2019 data as of 15 Jan 2019
**2019 data from 1-15 Jan 2019 only
Source: ESR

Table 3. Number of meningococcal disease cases by strain group 2017 and 2018

2017

Strain group	Age group						Total
	<1	1 to 4	5 to 9	10 to 14	15 to 19	20+	
Group B	**12**	**17**	**4**	**1**	**10**	**26**	**70**
B:P1.7-2,4	2	4	1	0	6	14	27
Other group Bs	10	13	3	1	4	12	43
Group C	**1**	**2**	**1**	**0**	**4**	**3**	**11**
C:P1.5-1,10-8	1	0	1	0	4	2	8
Other group Cs	0	2	0	0	0	1	3
Other	**1**	**2**	**0**	**2**	**1**	**18**	**24**
Group W	1	0	0	1	1	9	12
Group Y	0	2	0	1	0	8	11
Non-groupable	0	0	0	0	0	1	1

2018

Strain group	Age group						Total
	<1	1 to 4	5 to 9	10 to 14	15 to 19	20+	
Group B	**11**	**7**	**3**	**3**	**12**	**15**	**51**
B:P1.7-2,4	1	1	0	0	5	9	16
Other group Bs	10	6	3	3	7	6	35
Group C	**1**	**1**	**0**	**1**	**2**	**5**	**10**
C:P1.5-1,10-8	1	1	0	0	1	3	6
Other group Cs	0	0	0	1	1	2	4
Other	**4**	**5**	**5**	**1**	**4**	**33**	**52**
Group W	3	4	3	1	3	19	33
Group Y	1	1	1	0	0	13	16
Group X	0	0	0	0	0	1	1
Non-groupable	0	0	1	0	1	0	2

Meningococcal B Epidemic in New Zealand

From 1991 – 2007 New Zealand experienced a prolonged epidemic of meningococcal B, driven by a single group B subtype (B: P1.7-2,4), resulting in 6,128 cases and 252 deaths. The MeNZB vaccine was introduced from 2004 – 2008 to manage the epidemic and the number of disease notifications declined dramatically. The immune response to the vaccine was short-lived and it is not expected that anyone previously vaccinated would still have existing immunity to B disease.

The health need of the person

Survivors of IMD face a significant burden due to long-term physical, neurological and psychological sequelae which differ considerably in type, severity, duration and associated cost. IMD is a rapidly progressing and often fatal disease with death occurring in approximately 10% of patients. IMD is associated with significant morbidity with up to 20% of survivors of

IMD experiencing permanent sequelae including brain damage, adrenal impairment, hearing loss, renal failure and disfigurement. More than one third of survivors of childhood meningococcal B disease experience lifelong deficits such as psychological disorders, digit amputations, minor or unilateral hearing loss and minor communication deficits.

The availability and suitability of existing medicines, medical devices and treatments

There is currently no vaccine on the National Immunisation Schedule for the prevention of meningococcal group B disease.

The health need of family, whānau, and wider society

PHARMAC acknowledge that there may be a health need for other people as a result for caring for patients with IMD.

IMD is associated with significant mortality and morbidity and poses a significant burden on families and whānau. Long-term sequelae associated with IMD requires care from family and whānau members. This imposes a high burden associated with travel to from appointments, providing care and the potential need to cater to special needs by altering the home environment. Parents of children with severe IMD report experiencing psychological distress for months/years due to impact of the disease on the child and guilt associated with not recognizing the symptoms of the disease (Ehrlich et al., Pediatr Rehabil; 2005:220-4). There is a large emotional toll on the family or whānau as they cope with the loss of a family member due to IMD.

Due to the non-specific symptoms and rapid progression, IMD is often misdiagnosed which can also lead to considerable stress for healthcare workers.

The impact on the Māori health areas of focus and Māori health outcomes

Invasive meningococcal disease disproportionately affects those of Māori and Pacific descent with these populations exhibiting four times higher rates of meningococcal B disease across all age groups compared to the non-Māori/non-Pacific population from 2007–2016 children. Māori and Pacific infants <1 year of age had a six times higher rate of meningococcal B disease from 2007–2016 compared to non-Māori/non-Pacific Island children. The disproportionate distribution of IMD among Māori may be attributed to their low socioeconomic status and household crowding.

The impact on Pacific health areas of focus and Pacific health outcomes

Rates are highest in Pacific peoples. The disproportionate distribution of IMD among Pacific peoples may be attributed to their low socioeconomic status and household crowding.

The impact on the health outcomes of population groups experiencing health disparities

PHARMAC are not aware of any other population groups experiencing health disparities who are disproportionately affected by meningococcal B.

The impact on Government health priorities

This proposal relates to the Increased Immunisations Government health system priority through improved disease prevention.

Health Benefit

Details of the pharmaceutical under consideration

Clinical Pharmacology and Mechanism of Action

4CMenB is a multicomponent meningococcal group B vaccine containing purified recombinant meningococcal protein antigens consisting of four highly immunogenic components: three recombinant outer membrane proteins (neisserial heparin binding antigen [NHBA], neisserial adhesin A [NadA], and factor H binding protein [fHbp]) and outer membrane vesicles derived from *Neisseria meningitidis* group B strain NZ98/254.

Active immunisation against *N. meningitidis* group B strains may prevent meningococcal B infection and subsequent transmission.

New Zealand Regulatory Approval

Bexsero was approved for use in New Zealand by Medsafe in July 2018 for the following indications:

- for active immunisation against invasive disease caused by N. meningitidis group B strains; and
- for vaccination of individuals from 2 months of age and older.

Recommended Dosage and Treatment Paradigm

The applicant has proposed two dosing schedule options, 3+1 and 2+1.

- The 3+1 dosing schedule has the primary administrations at 6 weeks, 3 and 5 months and a booster at 12 months.
- The 2+1 dosing schedule has the primary administrations at 6 weeks and 3 months and a booster at 12 months.

With both dosing schedule proposals, the primary doses are aligned with the current National Immunisation Schedule (NIS), but the 12-month booster would be an additional visit which would result in additional work for vaccinators and increased vaccination claim costs for the Ministry of Health. The booster vaccination could be given at 15 months to align with the NIS,

but this would mean five injections would be given at the 15 months visit under the current schedule.

At its April 2018 meeting, the Immunisation Subcommittee recommended a 2 + 1 dosing schedule. Members noted that adding 4CMenB to the infant schedule would necessitate an additional immunisation visit at 12 months and changes to the infant schedule to ensure optimal vaccine combinations at each visit.

International Recommendations

Table 4: International recommendations regarding the funding of 4CMenB

Country	Vaccine	Programme
Australia	Bexsero	A state-wide meningococcal B immunisation programme for babies, as well as a catch up programme has been funded in South Australia since October 2018. An adolescent school-based immunisation programme will commence in February 2019, as well as a catch-up programme for those aged 17-20 years of age.
Canada	Bexsero	Meningococcal B vaccination has been funded since December 2014 for children at high risk of developing IMD.
England and Scotland	Bexsero	Meningococcal B vaccination has been part of the NHS routine childhood vaccination programme since September 2015.

The health benefits to the person, family, whānau and wider society

Evidence Summary

The supplier has identified three randomised, multicentre trials that provide the primary evidence for the safety and immunogenicity of 4CMenB for the prevention of IMD. A summary of these trials is provided below and the full papers are provided in Appendix 2.

Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunisation schedules *Gossger et al. JAMA 2012;307(6):573-82.*

A phase IIb, multicentre, open-label, parallel group, randomised controlled study of 1,885 infants enrolled at age 2 months. Participants were randomised into one of three groups to receive 4CMenB in combination with routine vaccines in varying schedules or to receive routine vaccines alone.

The main outcome measure was the percentage of participants with human complement serum bactericidal activity (hSBA) titre of 1:5 or greater against 3 Meningococcal B strains specific for vaccine antigens (NZ98/254, 44/76-SL and 5/99).

After three 4CMenB vaccinations, 99% or more of infants developed hSBA titres of 1:5 or greater against strains 44/76-SL and 5/99. For strain NZ98/254, this proportion varied and was 79%, 86.1% or 81.7% respectively for each dosing schedule.

The authors concluded that 4CMenB vaccine is immunogenic against reference strains when administered with routine vaccines at 2, 4 and 6 or at 2, 3 and 4 months of age, producing minimal interference with the response to routine infant vaccinations.

Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials *Vesikari et al. Lancet 2013;381:825-35*.

A phase III, partially-blinded, randomised, multicentre, controlled study to evaluate immunogenicity, safety and lot to lot consistency of 4CMenB vaccine when administered with routine infant vaccinations to healthy infants.

2,627 infants were enrolled in the open-label phase, 1003 in the observer-blind phase and 1,555 in the booster study. Lot-to-lot consistency was demonstrated for the three 4CMenB lots. Of 1,181 infants tested 1 month after three 4CMenB doses, 100% had hSBA titres of 5 or more for against strains selective for factor H binding protein and neisserial adhesin A, and 84% for New Zealand outer membrane vesicle.

Immune responses to routine vaccines were much the same with or without concomitant 4CMenB, but concomitant vaccination was associated with increased reactogenicity. 77% of infants had fever of 38.5 ºC or higher after any 4CMenB dose, compared with 45% after routine vaccines alone and 47% with MenC. Two febrile seizures were deemed probably related to 4CMenB.

The authors concluded that 4CMenB is immunogenic in infants and children aged 12 months with no clinically relevant interference with routine vaccines but increases reactogenicity when administered concomitantly with routine vaccines.

Reduced schedules of 4CMenB vaccine in infants and catch-up series in children: Immunogenicity and safety results from a randomised open-label phase IIIb trial *Martinon-Torres et al. Vaccine 2017;35:3548-57*.

A phase IIIb, open-label, multicentre study to evaluate the safety, tolerability and immunogenicity of 4CMenB when administered alone to healthy infants according to different immunisation schedules and to healthy children aged 2 to 10 years.

754 infants and 404 children were enrolled in this study. Sufficiency of immune responses was reported after two doses in 98-100% of infants receiving 2+1 schedules. Similarly, 95-99% of children demonstrated sufficiency of immune response following 2 catch-up doses.

A total of 45 serious adverse reactions were reported, of which 3 were considered related to vaccination.

International comparison

A 2+1 4CMenB schedule was funded in the UK national immunisation programme in September 2015, based on the 2012 rates of meningococcal B notifications for infants and children aged 1-4 years in the UK and Ireland (UK 22 and 7.6 per 100,000 respectively, Ireland

23 and 6.8 per 100,000 respectively). These rates are similar to those observed in New Zealand in 2007-2016 for infants (19.38 per 100,000) but lower than the same age group in Maori and Pacific Island populations (38.40 and 37.88 per 100,000 respectively).

In the first 10 months of the programme, cases of meningococcal B disease halved in vaccine eligible infants. Similar results were observed after adjustment for disease trends in the 4 years before vaccine introduction and in non-vaccine eligible children (Parikh et al. Lancet 2016; 388(10061): 2775-82.

Literature Search

PHARMAC staff conducted a PubMed search (search terms: 4CMenB) and identified the following additional publications regarding meningococcal B vaccination that were not identified by the supplier.

- De Serres et al. Short-term safety of 4CMenB vaccine during a mass meningococcal B vaccination campaign in Quebec, Canada. Vaccine; 2018:8039-46
- Macias Parra et al. Immunogenicity and safety of the 4CMenB and MenACWY-CRM meningococcal vaccines administered concomitantly in infants: A phase 3b, randomized controlled trial. Vaccine; 2018:7609-17.
- Biolchi et al. Evaluation of strain coverage of the multicomponent meningococcal serogroup B vaccine (4CMenB) administered in infants according to different immunisation schedules. Hum Vaccin Immunother; 2018. doi: 10.1080/21645515.2018.15377556
- Bryan P et al. Safety of multicomponent meningococcal group B vaccine (4CMenB) in routine infant immunisation in the UK: a prospective surveillance study. Lancet Child Adolesc Health; 2018:395-403.

Consequences for the health system

Dosing schedule

The applicant has proposed two dosing schedule options, 3+1 and 2+1. The 3+1 dosing schedule has the primary administrations at 6 weeks, 3 and 5 months and a booster at 12 months. The 2+1 dosing schedule has the primary administrations at 6 weeks and 3 months and a booster at 12 months. With both dosing schedule proposals, the primary doses are aligned with the current NIS, but the 12-month booster would be an additional visit which would result in additional work for vaccinators and increased vaccination claim costs for the Ministry of Health. The booster vaccination could be given at 15 months to align with the NIS, but this would mean five injections would be given at the 15 months visit under the current schedule.

Paracetamol administration

The applicant recommends prophylactic administration of paracetamol with every dose of 4CMenB to manage the known reactogenicity of the vaccine followed by two more doses 6 hours apart. Paracetamol is currently not recommended to be administered for childhood vaccinations, so this would represent an additional cost and increase in vaccinator workload to manage this. Vaccinators would need to be provided with training around the recommendation for prophylactic paracetamol.

Reduced Burden

The applicant considers that including 4CMenB in the NIS would reduce the burden on the healthcare system from the consequences of meningococcal infection, including reduced requirement for emergency transport to Starship ICU and reduced requirements for therapy associated with long term sequelae.

Suitability

The features of the medicine or medical device that impact on use

Pre-filled syringes

Bexsero is supplied as a 0.5 mL suspension in a pre-filled syringe (Type I glass) with a plunger stopper (Type I bromobutyl rubber) and with a protective tip cap (Type II rubber). Available pack sizes are one syringe with or without needles, or ten syringes without needles. Not all pack sizes may be distributed in New Zealand.

One dose (0.5 mL) contains:

Recombinant *Neisseria meningitidis* group B fHbp fusion protein	50 mcg
Recombinant *Neisseria meningitidis* group B NadA protein	50 mcg
Recombinant *Neisseria meningitidis* group B NHBA fusion protein	50 mcg
OMV from *Neisseria meningitidis* group B strain NZ98/254 measured as amount of total protein containing the Porin A (PorA P1.4)	25 mcg

Paracetamol use

The use of paracetamol to manage fever from the 4CMenB vaccine may impact on its suitability. Paracetamol use is not currently recommended for childhood immunisations and its use is important for managing the reactivity to the vaccine. Vaccinators and caregivers would need to be informed and prepared to administer paracetamol accordingly.

Costs and Savings

Costs and savings to pharmaceutical expenditure

Costs and savings will be considered in a separate paper to PTAC which will be written following the close of the Immunisation RFP on 18 January 2019.

Cost Effectiveness (combining the Health Benefits and Costs quadrants)

Cost effectiveness will be considered in a separate paper to PTAC which will be written following the close of the Immunisation RFP on 18 January 2019.

Appendix 1: May 2018 Immunisation Subcommittee meeting minutes

Appendix 2: Gossger et al. JAMA 2012;307(6):573-82.

Vesikari et al. Lancet 2013;381:825-35

Martinon-Torres et al. Vaccine 2017;35:3548-57

Parikh et al. Lancet 2016; 388(10061): 2775-82

THE FACTORS FOR CONSIDERATION

Factors are presented here in the order they appear in the paper, without implying any ranking or relative importance.

NEED

- The health need of the person
- The availability and suitability of existing medicines, medical devices and treatments
- The health need of family, whānau, and wider society
- The impact on the Māori health areas of focus and Māori health outcomes
- The impact on the health outcomes of population groups experiencing health disparities
- The impact on Government health priorities

HEALTH BENEFITS

- The health benefit to the person
- The health benefit to family, whānau and wider society
- Consequences for the health system

SUITABILITY

- The features of the medicine or medical device that impact on use by the person
- The features of the medicine or medical device that impact on use by family, whānau and wider society
- The features of the medicine or medical device that impact on use by the health workforce

COSTS AND SAVINGS

- Health-related costs and savings to the person
- Health-related costs and savings to the family, whānau and wider society
- Costs and savings to pharmaceutical expenditure
- Costs and savings to the rest of the health system

Technology Assessment Report No. 352

Rapid Economic Analysis on Bexsero® for meningococcal serogroup B

Last updated September 2020

Summary of Proposal

Table 11 - Proposal summary

Pharmaceutical Bexsero®
Supplier GlaxoSmithKline
Proposed Indication(s) Proposed indications considered in this report include the following sub-populations: 1. Infant '2+1' program. 2. Entrants to close living situations (13 to 25 years). 3. Entrants catch up for ages 13-25 years in close living situations for 1 year only and ongoing entrants as above. 4. Special high-risk immunocompromised groups - same as ACWY high risk criteria). 5. Close contacts of confirmed cases.
Dosing Dosing depends on patient population. For infants, 3 doses. For all other populations, 2 doses.
Pharmaceutical Price Proposed price of s9(2)(b) per dose for adolescent and infant proposals Proposed price of s9(2)(b) per dose immunocompromised and close contact proposals
Current Treatment Meningococcal disease can be treated with recommended antibiotics (benzyl penicillin and amoxycillin), but early treatment is vital. However, there are no vaccines currently available on the National Immunisation Schedule (NIS).

1 Executive Summary

June 2020 update.

PHARMAC staff updated the Meningococcal B incident rates for infants in the June prioritisation re-rank. In 2019 Men B cases in infants increased to 16 for the year, from 11 in 2018. In addition, the case fatality rate has been updated. In 2019 there was a total of 5 deaths from meningococcal B, which proportionally increased in comparison to total incident cases and so the CFR rate has increased from 5% in 2018 to 6.1%. Note the CFR rate is calculated from totalling all incident cases in the last 6 years and total deaths in the last 6 years.

These two factors, increased incidence and increased CFR rate have impacted the CUA ranges for the infant (2 + 1) proposal. Previously the likely and possible ranges on the OFI for the infant 2 + 1 proposal was s9(2)(b) and s9(2)(b), respectively. The likely range has increased to s9(2)(b) and the possible range has increased to s9(2)(b).

September 2020 update.

PHARMAC staff updated the incident rates to be informed by current incident trends and from available evidence for the proposal's: entrants to close living environments (13 to 25 years) no catch up, entrants to close living environments (13 to 25 years) plus catch up, special high-risk immunocompromised and close contacts. Previously the incident rates had been based on the infant incident rate and multiplied by un-justified multipliers.

Also, there is new evidence to inform that adolescents are likely to have protection from a vaccine for up to 7.5 years after the primary dose. Previously adolescent proposals (entrants to close living environments (13 to 25 years) no catch up, entrants to close living environments (13 to 25 years) plus catch up) had an assumed vaccine efficacy duration of 5 years, which has now been updated to 7 years in the model.

Further, the health utility for long-term sequelae and health sector costs have been updated as previously the calculation for these parameters had been incorrectly estimated. PHARMAC staff have since correctly estimated a weighted average estimate for both long-term sequelae health utility and health sector costs. The weighted average calculations are based on utility and cost figures provided by the supplier.

This Technology Assessment Report (TAR) summarises the incremental cost-effectiveness and budget impact of listing Bexsero® 4CMenB vaccine ('Bexsero') for meningococcal serogroup B for specific patient sub-populations. These estimates reflect the revised pricing proposals received from the supplier in December 2019. Specific sub-population programs considered in this TAR include:

1. Infant '2+1' program.
2. Entrants to close living situations (13 to 25 years).
3. Entrants catch up for ages 13-25 years in close living situations for 1 year only and ongoing entrants as above.
4. Special high-risk immunocompromised groups - same as ACWY high risk criteria.
5. Close contacts of confirmed cases.

Meningococcal disease is an infectious condition caused by Neisseria meningitidis, a gram-negative bacterium. Upwards 10% (or potentially more) of patients may die even with proper

medical care and up to 20% of survivors may have major permanent sequelae including brain damage, amputations, adrenal impairment, hearing loss, renal failure and disfigurement.

1.1 Cost Effectiveness

Indicative cost effectiveness results for these populations are summarised in Table 22.

Table 22 Summary: Indicative cost-effectiveness analysis for Bexsero for the above defined groups

Population groups	Likely QALYs per $m range
Infant '2+1' program.	s9(2)(b)
Entrants to close living situations (13 to 25 years).	s9(2)(b)
Entrants catch up for ages 13-25 years in close living situations for 1 year only and ongoing entrants as above.	s9(2)(b)
Special high-risk immunocompromised groups - same as ACWY high risk criteria).	s9(2)(b)
Close contacts of confirmed cases.	s9(2)(b)

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969). **Note* CUA results for immunocompromised groups and close contact proposals are reflective of a higher price s9(2) . The infant and adolescent proposals are reflective of a commercial price offer of approx. s9(2 per dose.**

Overall, the assumptions used for vaccine effectiveness and impact on case numbers may ultimately overstate the cost-effectiveness of vaccination. PHARMAC staff should consider revisiting the analysis should further data (including for efficacy and herd immunity) become available.

Cost-effectiveness results are sensitive to price, assumed annual seasonal incidence, the CFR and proportion of patients experiencing long-term sequelae.

PHARMAC staff reviewed the submitted supplier model and consider it as conceptually appropriate. The submission specifically evaluated an infant's (i.e., under 12 months age) vaccination program. PHARMAC staff noted the model's use and acceptance in the United Kingdom and Australia, with modified variables populated reflecting the New Zealand clinical and epidemiological environment largely populated in the model by the supplier.

The supplier submission estimated the cost per quality adjusted life year (QALY) of the infant '2+1' program at s9(2)(b)(ii), (for a '2+1' program) and s9(2)(b)(ii), ('3+1' program) (or s9(2) to s9(2) QALYs per $1m).

Acknowledging the need for simplicity, reproducibility of outcomes and to facilitate comparative decision making, PHARMAC staff have prepared their own simplified cost-utility analyses models for the patient groups.

Following consideration of expert clinical advice, PHARMAC's PFPA and New Zealand-specific issues, PHARMAC staff considered the following adaptations to analysis assumptions appropriate:

- Change the base case infant program from a '3+1' to a '2+1' program. '3+1' refers to infant doses at 6 weeks, 3 months, and 5 months, with a 'booster dose' at 12 months; '2+1' refers to doses at 6 weeks and 3 months, with a 'booster dose' at 12 months.
- The supplier assumed the vaccine had efficacy against meningococcal carriage acquisition of 26.6%; following advice from PHARMAC's Pharmacology and Therapeutics Advisory Committee (PTAC), this was reduced to 0% (see Section 4.2.1.3 for more details). This means no herd immunity effect is assumed.
- Use of quality of life adjustment factors (QAFs). Reflecting the approach used by the UK's Joint Committee on Vaccination and Immunisation (JCVI) (see 5.2 for further details), the supplier applied a QAF of 3 to reflect the severity of the condition. PHARMAC, in accordance with its methodological approach to pharmacoeconomic analysis outlined in the Prescription for Pharmacoeconomic Analysis (PFPA), does not practise this and so it was excluded from input assumptions.
- Removing double-counting of the impact of long-term caregiving. The original supplier model assumed both a reduction in caregiver utility and a direct cost for caregiving of those patients with long-term sequelae. Methodologically this is inappropriate; only utility or cost impacts should be captured. PHARMAC modelling subsequently assumed only costs.

PHARMAC staff note there to be no direct evidence of benefit for universal childhood vaccination. A 3-year surveillance study of the safety and effectiveness of the UK 4CMenB infant vaccination programme in England estimated it to be 82.9% effective in preventing disease in infants aged younger than 12 months. Analysis in this TAR assumes this efficacy for all patient populations. This limited evidence and uncertainty has implications for interpretation of results (see Section 1.3).

1.2 Budget Impact

Table 33 summarises the yearly DHB (vaccine dose plus administration) budget impacts for each sub-population. Budget impact is driven by the level of vaccine uptake. For infants and young children, an uptake rate of 90% is assumed, for adolescents and young adults, 75% is assumed.

Table 33 Summary of total DHB budget impact for each sub-population: cost of vaccine program implementation: vaccine and administration

Population group	Year 1	5-year NPV
Infant '2+1' program.	s9(2)(b)(ii),	s9(2)(b)(ii),
Entrants to close living situations (13 to 25 years).	s9(2)(b)(ii),	s9(2)(b)(ii),
Entrants catch up for ages 13-25 years in close living situations for 1 year only and ongoing entrants as above.	s9(2)(b)(ii),	s9(2)(b)(ii),
Special high-risk immunocompromised groups - same as ACWY high risk criteria.	s9(2)(b)(ii),	s9(2)(b)(ii),
Close contacts of confirmed cases.	s9(2)(b)(ii),	s9(2)(b)(ii),

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969) Notes: Individual year amounts undiscounted. Amounts rounded to nearest thousand dollars. These represent the estimated budget impact of individual vaccination programs implemented in isolation; no assumption of interactive budget effects due to simultaneously administered programs is assumed.
Note* CUA results for immunocompromised groups and close contact proposals are reflective of a higher price s9(2)(b) Other proposals are reflective of a commercial offer of approx. s9(2 per dose.

Table 44 summarises the net change in health care resource utilisation costs for each scenario. These reflect savings to the DHB health care system from reduced acute hospitalisation and management of long-term sequelae.

Table 44 Summary of DHB budget impact for each patient sub-population: change in health care resource utilisation costs

Population group	Year 1	5-year NPV
Infant '2+1' program.	-$171,000	$2,170,000
Entrants to close living situations (13 to 25 years).	$224,000	$850,000
Entrants catch up for ages 13-25 years in close living situations for 1 year only and ongoing entrants as above.	$1,000,000	$1,680,000
Special high-risk immunocompromised groups - same as ACWY high risk criteria.	$72,000	$194,000
Close contacts of confirmed cases.	$11,000	$45,000

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969) Notes: Individual year amounts undiscounted. Amounts rounded to nearest thousand dollars. These represent the estimated budget impact of individual vaccination programs implemented in isolation; no assumption of interactive budget effects due to simultaneously administered programs is assumed.

Error! Not a valid bookmark self-reference. summarises the overall net DHB change in health care resource utilisation costs associated with listing each scenario (i.e., implementation costs offset by health care resource utilisation costs saved).

Table 55 Summary of DHB budget impact for each sub-population: aggregate of vaccine program implementation and change in health care resource utilisation costs

Population group	Year 1	5-year NPV
Infant '2+1' program.	s9(2)(b)(ii),	s9(2)(b)(ii),
Entrants to close living situations (13 to 25 years).	s9(2)(b)(ii),	s9(2)(b)(ii),
Entrants catch up for ages 13-25 years in close living situations for 1 year only and ongoing entrants as above.	s9(2)(b)(ii),	s9(2)(b)(ii),
Special high-risk immunocompromised groups - same as ACWY high risk criteria.	s9(2)(b)(ii),	s9(2)(b)(ii),
Close contacts of confirmed cases.	s9(2)(b)(ii),	s9(2)(b)(ii),

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969) Notes: Individual year amounts undiscounted. Amounts rounded to nearest thousand dollars. These represent the estimated budget impact of individual vaccination programs implemented in isolation; no assumption of interactive budget effects due to simultaneously administered programs is assumed. **Note* CUA results for immunocompromised groups and close contact proposals are reflective of a higher price s9(2)(b) Other proposals are reflective of a commercial offer of approx. s9(2 per dose.**

1.3 Limitations and Interpretations

Results are subject to several limitations and caveats in interpretation including:

- Tracing and predicting the spread of infectious diseases in a population is highly complex. There is a considerable number of epidemiological factors influencing disease spread and the consequent number of assumptions required to be incorporated in economic modelling to capture all key drivers of outcomes. As such, their collective impact on final cost-effectiveness results are presented as ranges for the respective population groups. PHARMAC staff should consider revisiting analysis should assumptions or inputs (e.g. herd immunity) change over time.
- Meningococcal disease is seasonal in nature and severity and as such cost-effectiveness is dependent on the seasonal incidence in given patient sub-populations. Analysis in this TAR is based on meningococcal cases and sequelae experienced to date in New Zealand. Again, PHARMAC staff should consider revisiting analysis should assumptions or inputs regarding seasonal incidence, including severity, change over time.
- The lack of direct evidence from randomised controlled trials that Bexsero vaccination reduces rates of IMD. Effectiveness estimates, including duration, are based on a surveillance study of infants only. This is best available evidence but has the potential to overstate cost-effectiveness results. PHARMAC staff should consider revisiting analysis should new evidence become available.
- Cost-effectiveness results are presented as single ranges, but this obscures the fact that cost-effectiveness changes over time. An effective vaccination program that

reduces incident cases means there is a reduced number of infected individuals in the population and a smaller 'pool' of at risk patients. The subsequent annual vaccination of additional 'new' population cohorts every year reduces the susceptibility of the population to infection. Over time, this would likely result in the prevention of fewer and fewer cases meaning consequently each year is incrementally less cost-effective.

- Estimates of cost-effectiveness reflect the current mix of B strains; it is acknowledged these can change over time impacting the cost-effectiveness and budgetary impact of proposals.
- Further, for smaller sub-populations, the value of some of these input assumptions are uncertain or there is limited evidence for them. This results in a wide range of potential cost-effectiveness outcomes between the patient populations, reflecting uncertainty about key input assumptions due to lack of specific evidence relevant to the analysis in question (e.g. greater incidence risk inherent in close living populations).
- Budget impact is influenced by both trends in uptake and vaccine pricing. Demand for vaccines worldwide is currently high, shaping available stock and pricing dynamics. Rates of uptake will change the budget impact of any given program. Both of these in turn will also influence any program's cost-effectiveness.

2 Context

2.1 Background

PHARMAC took over management of vaccines in July 2012. In October 2012, supplier Te Arai Biofarma proposed their meningococcal vaccine be listed on the Pharmaceutical Schedule. In April 2013, the Immunisation Subcommittee ('Subcommittee') recommended that PHARMAC prepare a paper on universal meningitis C vaccination (Objective ID A619944).

PHARMAC conducted a Request for Proposal (RFP) in June 2013 and in December the PHARMAC Board approved funding of two meningococcal C vaccines: Neisvac-C, and Menactra, the latter also protecting against A, Y, and W-135 strains. These vaccines were listed from July 2014 subject to the following restrictions:

Any of the following:

1. *One dose for patients pre- and post-splenectomy; or*
2. *One dose every five years for patients with functional asplenia or post solid organ transplant; or*
3. *One dose for close contacts of meningococcal cases; or*
4. *A maximum of two doses for bone marrow transplant patients; or*
5. *A maximum of two doses for patients following immunosuppression*.

2.2 Proposal Under Assessment

In February 2018, PHARMAC received an application from the supplier for the listing of Bexsero as an infant (i.e., under 12 months) vaccination program (Objective ID A1117983). This was proposed for implementation as either a '2+1' or a '3+1' program (with the '1' being a booster dose).

In May 2018, the Subcommittee gave the proposal a medium recommendation (Objective ID A114825) as follows:

- The Subcommittee recommended that 4CMenB be funded for universal infant vaccination as part of the Infant Immunisation Schedule, with a 2+1 dosing schedule, with a medium priority.
- The Subcommittee recommended that 4CMenB be funded with a medium priority for high risk groups and close contacts, based on high clinical need.

In November 2018, PHARMAC commenced a Request for Proposal (RFP) process for vaccines. In February 2019, PTAC also gave medium recommendations for infants and close-living sub-populations. PTAC referred to the Subcommittee for discussion and confirmation specific issues such uptake rates, efficacy, and herd immunity (Objective ID A1223390).

In March 2019, the Subcommittee gave advice to PHARMAC staff on these matters (Objective ID A1246094). These issues are detailed later in this TAR. The Subcommittee recommended the vaccination with low priority for infants, as a high-priority for special high risk

immunocompromised patients (as defined by the current meningococcal ACWY access criteria), as a medium priority for close contacts of meningococcal B cases and previous cases and as a high priority for those adolescents and young adults aged 13 to 25 in close living situations, with a one-year catch-up program due to the higher risk presented. In March 2019, PHARMAC staff subsequently decided to proceed with assessing these as individual proposals, as outlined in this TAR.

In summary these population groups are:

1. Infant '2+1' program.
2. Entrants to close living situations (13 to 25 years).
3. Entrants catch up for ages 13-25 years in close living situations for 1 year only and ongoing entrants as above.
4. Special high-risk immunocompromised groups - same as ACWY high risk criteria.
5. Close contacts of confirmed cases.

In December 2019, the supplier proposed a revised net price of s9(2) per dose, a s9(% reduction from the original s9(2) per dose considered in original assessment. This TAR assesses the impact of this reduction on the infant and adolescent proposals, in addition the smaller proposals (immunocompromised and close contacts) have been assessed with the original price of s9(2)(b) as they are being prioritised separately.

2.3 Proposed Pharmaceutical Under Assessment

Bexsero is a 0.5 mL suspension in a pre-filled syringe (Type I glass) with a plunger stopper (Type I bromobutyl rubber) and with a protective tip cap (Type II rubber). Pack sizes of one syringe with or without needles or ten syringes without needles. Not all pack sizes may be distributed in New Zealand. One dose (0.5 mL) of 4CMenB contains:

- Recombinant Neisseria meningitidis group B fHbp fusion protein*† 50 µg
- Recombinant Neisseria meningitidis group B NadA protein*† 50 µg
- Recombinant Neisseria meningitidis group B NHBA fusion protein*† 50 µg
- OMV from Neisseria meningitidis group B strain NZ98/254 measured as amount of total protein containing the Porin A (PorA P1.4) † 25 µg

2.4 Current Treatment in New Zealand

'Treatment' of infectious diseases such as meningococcal is most appropriately considered as prophylactic protection from infection. Treatment for confirmed cases is available in New Zealand; recommended antibiotics include benzyl penicillin and amoxycillin (Meningitis NZ), but early treatment is vital. However, there are no vaccines currently available on the National Immunisation Schedule (NIS).

3 Disease

3.1 Description of Disease

Meningococcal disease is an infectious condition caused by Neisseria meningitidis, a gram-negative bacterium. Asymptomatic nasopharyngeal carriage of pathogenic meningococci is common, especially among adolescents. Carriage can lead (but not always) to invasive meningococcal disease (IMD) both in carriers and other individuals.

Transmission occurs from person to person by respiratory droplets or direct contact with nasopharyngeal secretions, from a carrier or an IMD case, including by coughing or sneezing, kissing and sharing eating or drinking utensils, toothbrushes and pacifiers (New Zealand Ministry of Health, 2018). This method of transmission is common for all serogroups of meningococcal.

IMD causes inflammation and swelling of the meninges – the membranes that surround the brain and spinal cord. It can also go on to cause septicaemia (severe blood poisoning) (Southern Cross New Zealand, 2018).

IMD is easily misdiagnosed, progressing from non-specific symptoms, such as fever and irritability, to death within 24 hours of onset, even with medical intervention. This rapid progression leaves clinicians with a narrow window for diagnosis and intervention.

Cases of IMD are rapid and can be fatal, while also having severe implications for survivors' functioning and lifelong health related quality of life (HRQoL). Approximately 10% (or potentially more) of patients may die even with proper medical care and up to 20% of survivors may have major permanent sequelae including brain damage, amputations, adrenal impairment, hearing loss, renal failure and disfigurement (Southern Cross New Zealand, 2018). It should be noted that rates of mortality and sequelae for meningococcal B are higher than that associated with meningococcal W and Y.

3.2 Epidemiology

June 2020 - update

Table *66* below has been updated to reflect incident cases in 2019. Men B cases have increased in 2019 to 62 total cases, from 51 in 2018.

Table *88* below has been updated to reflect incident Men B cases by age group. Note the increase of infant cases to 16 in 2019 from 11 in 2018. This has caused the incident rate per 60,000 estimated infants to increase from 0.0183% in 2018 to 0.0267% in 2019. This has subsequently impacted the CUA ranges which are sensitive to the incident rate parameter.

Meningococcal disease is seasonal, and incidence may vary year to year based on numerous factors including prevailing serogroups and strains of these serogroups, their severity, carriage prevalence, population contact (between respective demographics in the population) and existing levels of vaccination. Incidence may also vary worldwide; for example, incidence rates in New Zealand are currently around 2 per 100,000 (ESR, 2018); in the UK this rate is currently at 1 in 100,000 (Public Health England, 2018).

Further, incidence will vary by age in a given population; typically, incidence is highest in infants and adolescents, however this may change with different serogroups and the nature and virulence of given seasonal strains. Worldwide, the most important serogroups of meningococci are A, B, C, W and Y.

Historically, the incidence of meningococcal disease in NZ has been predominantly caused by meningococcal serogroups B and C. The meningococcal epidemic in New Zealand between 1991 and 2007 was primarily attributable to serogroup B meningococci expressing the P17b,4 (P1. 7-2,4) PorA protein. Following the introduction of MeNZB™ in 2002 to specifically address the outbreak, the proportion of B cases has steadily declined. Cases of W and Y have increased in recent years. Groups W and Y have accounted for more cases than C since 2017. Mortality and morbidity associated with meningococcal C and W is higher than that associated with meningococcal B.

In 2018, 120 cases of meningococcal disease were notified in New Zealand, which was higher than the 105 cases in 2017 and continues an increasing trend since the low of 36 cases reported in 2014. It should be noted that the proportion of laboratory confirmed cases is extremely high for meningococcal, with only 2.5% of all cases in 2018 considered 'probable'. Of the 120 cases in 2018, 10 mortalities resulted, with six of these being from W cases.

However, the number of cases in 2018 remains significantly lower than the 647 cases in 2001 during the meningococcal disease epidemic (driven by the B:P1.7-2,4 strain) (ESR report available online: https://surv.esr.cri.nz/PDF_surveillance/AnnualRpt/AnnualSurv/2016/NotifiableDiseaseReportCommentary2016.pdf).

In 2018, 55% of identified cases were for non-B disease, with Group W being the most prevalent of the non-B groups (**Table 66**). It should be noted that no cases of serogroup A have been recorded. In the year to 31 March 2019, 19 cases have been laboratory-confirmed, with 21% group W and 63% being group B.

Table 66 Meningococcal disease cases by group by year, 2013-2019

Strain group	Year						
	2013	2014	2015	2016	2017	2018	2019*
Group B	**30**	**26**	**41**	**47**	**70**	**51**	**62**
B: P1.7-2,4	11	13	10	23	27	16	19
Other group Bs	19	13	31	24	43	35	43
Group C	**17**	**6**	**6**	**8**	**11**	**10**	**7**
C: P1.5-1,10-8	15	5	3	4	8	6	7
Other group Cs	2	1	3	4	3	4	0
Other	**11**	**4**	**12**	**12**	**24**	**52**	**53**
Group W	5	0	6	5	12	33	36
Group Y	4	3	6	7	11	16	16
Group E	0	1	0	0	0	0	1
Group X	0	0	0	0	0	1	0
Non-groupable	2	0	0	0	1	2	6

Total	**58**	**36**	**59**	**67**	**105**	**113**	**122**

Source: ESR (https://surv.esr.cri.nz/surveillance/Meningococcal_disease.php)
Notes: *2019 data to 31 March 2019. 2018 cases not included here include 4 'other lab-confirmed' cases where no group or other strain characteristics were determined and 3 'probable' cases.

These 'other' cases have tended to be more predominant in those 20 years of age or older, but those cases with higher morbidity and mortality tend to be in those under one year of age. The number of cases of all groups by age in 2018 and 2019 are shown in **Table *77*** and **Table *88*** respectively.

Table 77 Meningococcal cases by serogroup and age, 2018

Strain group	Age group						Total
	<1	1 to 4	5 to 9	10 to 14	15 to 19	20+	
Group B	**11**	**7**	**3**	**3**	**12**	**15**	**51**
B: P1.7-2,4	1	1	0	0	5	9	**16**
Other group Bs	10	6	3	3	7	6	**35**
Group C	**1**	**1**	**0**	**1**	**2**	**5**	**10**
C: P1.5-1,10-8	1	1	0	0	1	3	**6**
Other group Cs	0	0	0	1	1	2	**4**
Other	**4**	**5**	**5**	**1**	**4**	**33**	**52**
Group W	3	4	3	1	3	19	**33**
Group Y	1	1	1	0	0	13	**16**
Non-groupable	0	0	0	0	0	1	**1**
Non-groupable	0	0	1	0	1	0	**2**
Total	**16**	**13**	**8**	**5**	**18**	**53**	**113**

Source: ESR (https://surv.esr.cri.nz/surveillance/Meningococcal_disease.php)

Table 88 Meningococcal cases by serogroup and age, 2019

Strain group	Age group						Total
	<1	1 to 4	5 to 9	10 to 14	15 to 19	20+	
Group B	**16**	**10**	**6**	**3**	**9**	**18**	**62**
B: P1.7-2,4	4	2	0	0	4	9	**19**
Other group Bs	12	8	6	3	5	9	**43**
Group C	**0**	**0**	**2**	**0**	**2**	**3**	**7**
C: P1.5-1,10-8	0		2		2	3	**7**
Other group Cs	0	0	0	0	0	0	**0**
Other	**9**	**6**	**2**	**0**	**4**	**32**	**53**
Group W	8	5	1	0	2	20	**36**
Group Y	1	1	1	0	1	12	**16**
Group E	0	0	0	0	1	0	**1**
Non-groupable	0	0	0	0	0	0	**0**
Total	**25**	**16**	**10**	**3**	**15**	**53**	**122**

Source: ESR (https://surv.esr.cri.nz/surveillance/Meningococcal_disease.php)

Table 99 summarises meningococcal notifications by serogroup and DHB for calendar year 2018. Geographically, 60% of cases were concentrated in the top half of the northern island (Northland, Waitemata, Auckland, Counties Manukau, Waikato and Bay of Plenty).

Table 99 Meningococcal disease notifications by DHB, 1 Jan–31 Dec 2018

District Health Board	Group						Other lab-confirmed[2]	Probable[3]	Total	Rate per 100,000*
	B	W	Y	C	X	NG[1]				
Northland	0	7	3	1	0	0	1	1	13	7.4
Waitemata	3	5	2	2	1	0	0	0	13	2.1
Auckland	5	4	1	1	0	0	0	1	12	2.3
Counties Manukau	9	2	1	0	0	0	1	0	13	2.4
Waikato	3	0	0	4	0	1	0	0	8	2.0
Lakes	0	2	1	0	0	0	0	0	3	2.8
Bay of Plenty	5	2	0	1	0	0	1	1	10	4.3
Tairawhiti	1	0	0	0	0	0	0	0	1	2.1
Taranaki	3	0	0	1	0	0	0	0	4	3.4
Hawke's Bay	0	0	0	0	0	0	0	0	0	0.0
Whanganui	2	1	0	0	0	0	0	0	3	4.7
MidCentral	1	1	2	0	0	0	0	0	4	2.3
Hutt Valley	1	0	0	0	0	1	0	0	2	1.4
Capital & Coast	4	2	0	0	0	0	0	0	6	1.9
Wairarapa	0	0	1	0	0	0	0	0	1	2.2
Nelson Marlborough	2	0	2	0	0	0	0	0	4	2.7
West Coast	0	0	0	0	0	0	0	0	0	0.0
Canterbury	4	3	2	0	0	0	1	0	10	1.8
South Canterbury	0	1	0	0	0	0	0	0	1	1.7
Southern	8	3	1	0	0	0	0	0	12	3.7
Total	**51**	**33**	**16**	**10**	**1**	**2**	**4**	**3**	**120**	**2.5**

Source: ESR, 2019 (https://surv.esr.cri.nz/surveillance/Meningococcal_disease.php).

The increase in serogroup W cases reflects the experience in Australia, where W became the predominant group in 2016 and 2017 (109 and 141 cases respectively reported to the National Notifiable Diseases Surveillance systems (NNDSS)).

While most group W cases in Australia have been reported in adults, there has been an increase in cases in children aged less than 5 years. Many of the group W cases belong to a hypervirulent sequence type (ST-11), associated with a higher risk of invasive disease and a higher CFR. A similar increase in group W cases has also been reported in the United Kingdom (210 cases in 2015/16) (ESR 2016 Annual Surveillance report).

4 Economic Analysis

Economic analysis of infectious diseases is complex, both with respect to model structure and the need to use numerous input assumptions. Section 4.1 outlines the scope of the analysis. Section **Error! Reference source not found.** describes the model structure of the supplier-submitted economic evaluation and subsequent PHARMAC adaptation to create a simpler, more reproducible model that facilitates comparison of patient populations. Section 4.3 details key event probabilities. Section 4.4 outlines key population cohorts. Section 4.5 outlines key uptake assumptions. Section 4.6 details patient population definitions. Section 4.7 details vaccine efficacy assumptions. Section 4.2.1.2 addresses the issue of carriage. Section 4.2.1.3 addresses the issue of herd immunity. Section 4.2.1.4 outlines assumptions for population contacts. Section 4.8 specifies utility values used for the defined health states and Section 0 details costs employed in the model.

It should be noted only key assumptions and inputs are discussed in this TAR. For further information on all assumptions, refer to “Attachment 03a_HE Model” (Objective ID A1118195) and “Budget Impact Analysis work up for Meningococcal” (Objective ID A1255755).

4.1 Scope of Analysis

4.1.1 Decision Problem and Perspective

The decision problem is determining the incremental cost-effectiveness of listing Bexsero vaccine for meningococcal serogroup B for specific age-based sub-populations in New Zealand.

Analyses conducted are for vaccination of individual sub-populations, without consideration of cost-effectiveness of funding more than one sub-population concurrently.

This analysis was conducted from perspective of the public health system, as per the PFPA version 2.2. (2015).

4.1.2 Populations under Assessment

As per Section 2.2, listing Bexsero for meningococcal serogroup B. Specific sub-populations individually considered in this TAR include the following:

1. Infant ‘2+1’ program.
2. Entrants to close living situations (13 to 25 years).
3. Entrants catch up for ages 13-25 years in close living situations for 1 year only and ongoing entrants as above.
4. Special high-risk immunocompromised groups - same as ACWY high risk criteria).
5. Close contacts of confirmed cases.

4.1.3 Comparator

As per section 0, there are currently no vaccines available for the prevention of meningococcal in the specified sub-populations. The treatment and comparator arms are as follows for all patient sub-populations:

Bexsero vaccination vs. No vaccination

4.2 Economic Model

PHARMAC staff subsequently reviewed the supplier model as part of formal assessment of the application.

The supplier employed a model that was originally adapted from a 2006 model developed for meningococcal C. The model has been previously used and accepted in many other countries including the UK and Australia.

Section **Error! Reference source not found.** describes the structure of the model as submitted by the supplier. Included are explanations of three key underpinning concepts which reflect meningococcal aetiology and how they are accounted for by the model:

- Carriage
- Herd immunity
- Population physical contact which spreads the disease, i.e. contact matrices

Section 4.2.2. details PHARMAC review and critique of the model. Section 4.2.3 outlines the PHARMAC developed model structure employed in the subsequent economic analysis.

4.2.1 Description of Model Structure: Supplier Model

Description of the model structure benefits from firstly describing the aetiology of meningococcal disease. Asymptomatic nasopharyngeal carriage of bacterium is common, especially among adolescents, and is transmitted through interpersonal contact. Carriers are therefore reservoir of pathogenic meningococci which can lead to invasive disease. However, being a carrier does not mean a person will develop IMD.

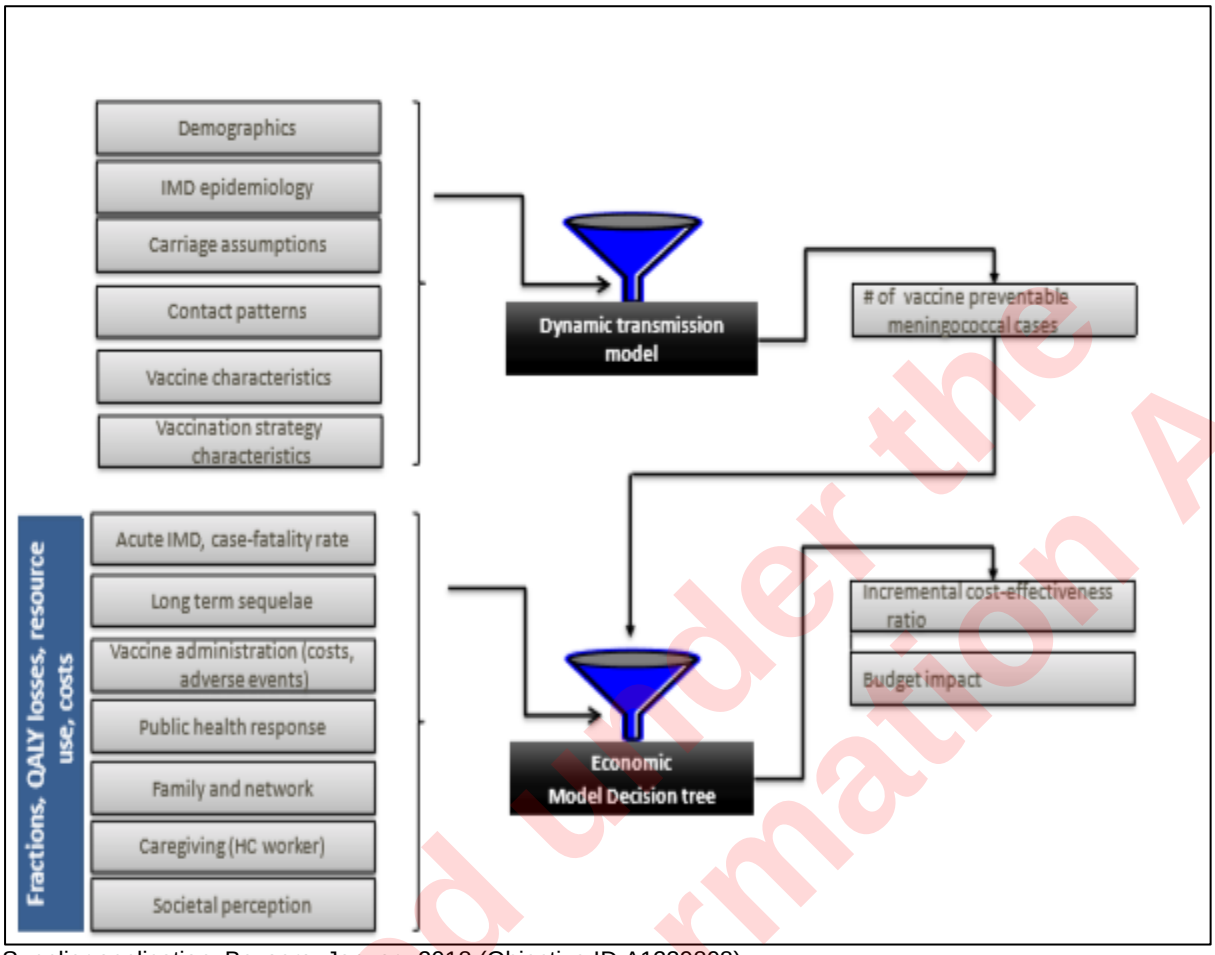
The model assesses the impact of vaccination on direct prevention of disease cases, and on carriage. The interaction between infection (carriage) and disease (cases) is considered in the dynamic transmission model, which in turn affect the probability of developing IMD.

To examine the cost-effectiveness a two-stage health economic model is used:

1. Dynamic transmission model to simulate transmission of meningococcus carriage over time and to estimate cases of vaccine-preventable IMD (all serogroups).
2. Decision tree to estimate cost-effectiveness of vaccination; costs and health outcomes associated with cases of IMD in vaccine versus standard care arms.

Figure 11 gives an overview of these two steps.

Figure 11 Overview of the economic evaluation steps



Supplier application, Bexsero, January 2018 (Objective ID A1239808)

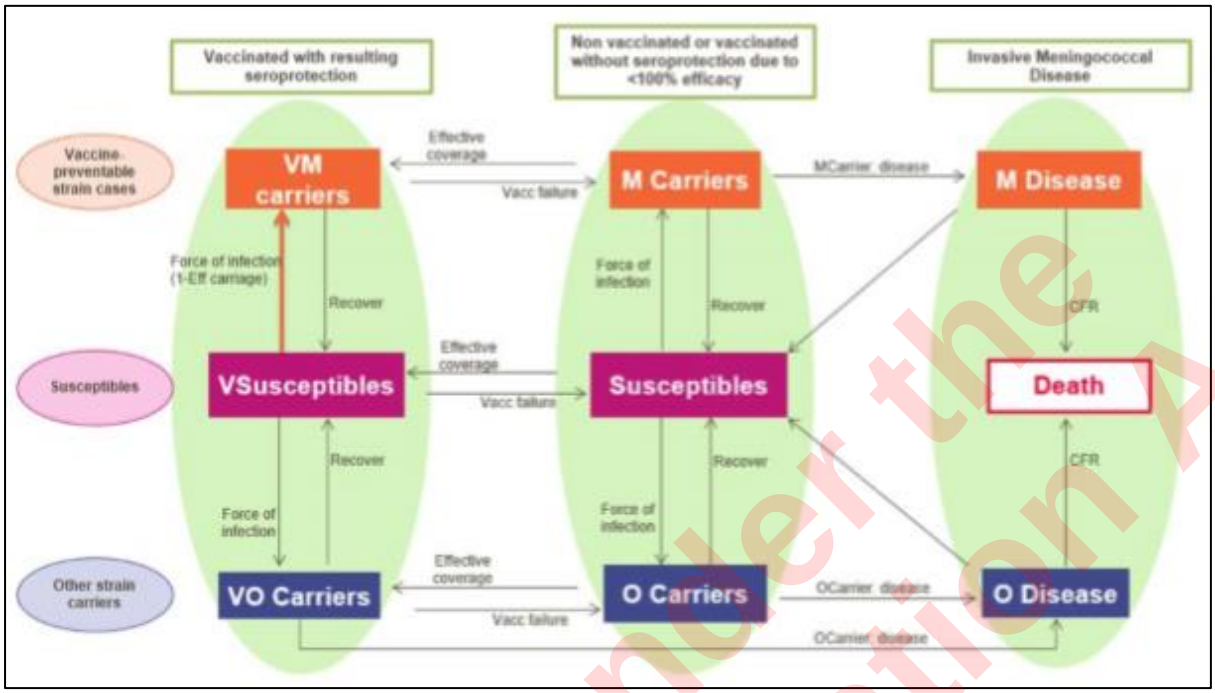
4.2.1.1 Dynamic Transmission Model

The model is based on the dynamic transmission model developed by Huels et al (2014), which used the structure of a published meningococcal serogroup C disease transmission model by Trotter et al (2006).

The model has been previously used and accepted in many other countries including the UK and Australia and has been adapted for New Zealand in this analysis. The model is dynamic in that the force of infection changes over time based on rates of carriage in the population; while rates of carriage change with the force of infection.

By using this structure, the vaccine's protection against carriage acquisition can be estimated. The underlying disease transmission process is a susceptible-infected-susceptible (SIS) model. The dynamic transmission part of the model consists of mutually exclusive compartments for vaccine-preventable or non-vaccine preventable meningococcal carriage and vaccination status. Individuals move across compartments as per the Huels et al (2014) model structure (
Figure *22*).

Figure 22 Dynamic model structure



Source: Supplier application, Bexsero, January 2018 (Objective ID A1239808)

At the model's starting point, subjects are distributed across compartments based on assumptions regarding current prevalence of vaccination, infection, and disease. In the diagram, the first column represents seroprotected subjects, the second non-seroprotected and the third those with IMD. The top row represents subjects infected with vaccine-preventable meningococcus, the second uninfected subjects susceptible to infection, and the third, subjects infected with non-vaccine-preventable meningococcus.

All compartments are repeated for each one-year age group for ages 0 to 99 years. Subjects age each year, with a maximum life expectancy of 100 years for those not dying of IMD or another condition. Each year, a new birth cohort enters the 'non-vaccinated susceptibles' (S) compartment.

During each cycle, proportions of subjects reaching certain defined ages are vaccinated and, depending on the likelihood of a successful vaccination, move from susceptible (S) to susceptible – seroprotected (SR) or from infected to infected – seroprotected (O to OR or M to MR, depending on whether the meningococci is vaccine-preventable or not). A proportion of carriers of a vaccine preventable meningococcus (M) may recover spontaneously immediately upon vaccination and become susceptible – seroprotected.

During each model cycle, susceptible subjects (SR, S) may become infected and acquire carriage of a vaccine-preventable meningococci (M) or a non-vaccine-preventable meningococci (O), and subsequently transition to the infected compartment corresponding to their vaccination status. Most carriers of vaccine-preventable or non-vaccine-preventable meningococci recover and return to the susceptible state after several months. A small proportion develop vaccine-preventable disease (M Disease) or non-vaccine-preventable

meningococci (O Disease). Subjects who recover from IMD return to the non-vaccinated susceptible state. Subjects with IMD can also die.

An underlying assumption of the model is that successful vaccination may confer some protection against carriage acquisition, and that it confers complete protection against vaccine-preventable IMD.

Patients in the treatment arm may be vaccinated (with Bexsero) or not; those in the comparator arm are universally unvaccinated. Those vaccinated may be afforded direct protection or still be at risk of being infected. The aggregate of those directly protected are the resulting 'total effectively protected' population.

Those with meningococcal are hospitalised for acute care and subject to the risk of mortality or long-term sequelae. Those who have acute cases only incur a quality of life decrement for the period of the event (including hospitalisation) and those who experiencing long term sequelae experience permanent long-term reduction in quality of life.

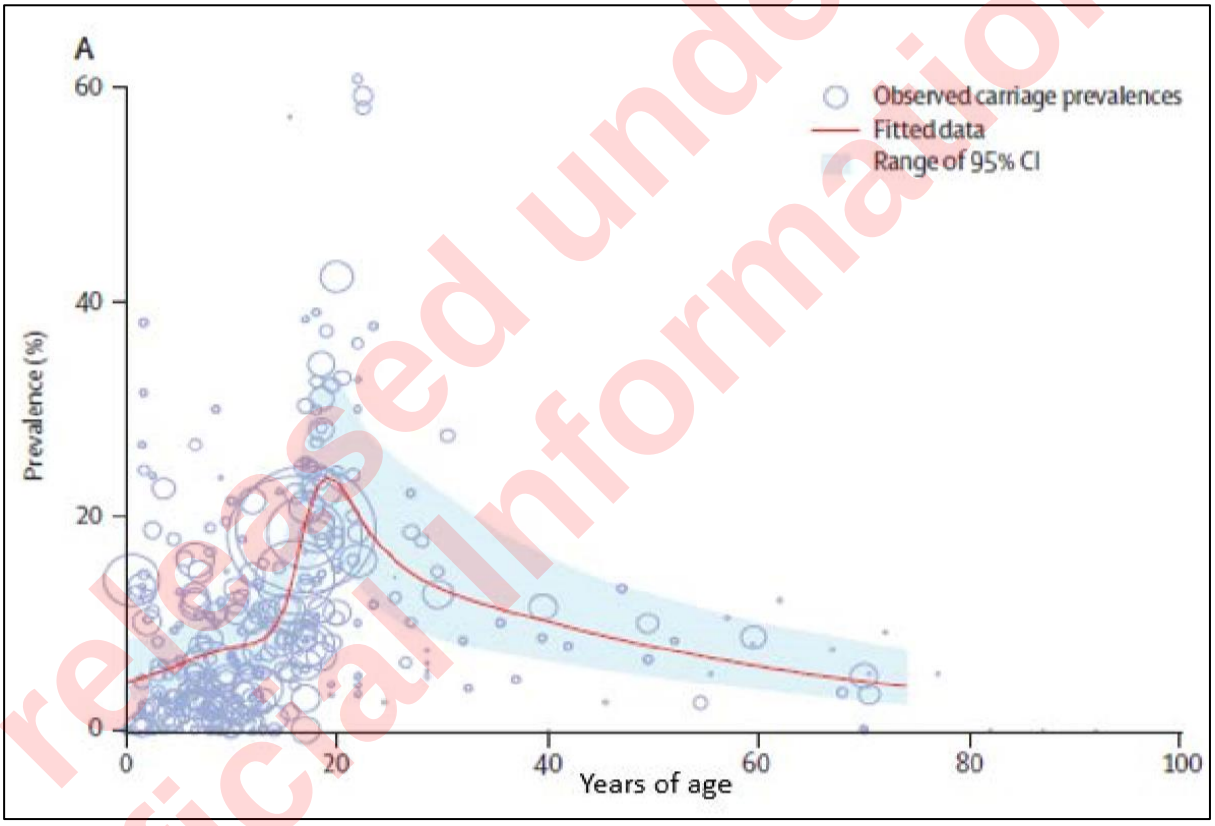
The model considers the overall population in question, rather than just the individual. Should any vaccine program be implemented, it is assumed to occur annually and is unaffected by the specific individuals in the given sub-population; rather, the program is driven by patient's membership in the defined sub-population (individuals may move in and out of the defined population, but the population remains). As such, a lifetime model is employed.

4.2.1.2 Carriage

Asymptomatic nasopharyngeal carriage of bacterium is common, especially among adolescents, and is transmitted through interpersonal contact. Carriers are therefore reservoirs of pathogenic meningococci which can lead to IMD. Christensen et al (2010) estimated the age-specific prevalence of meningococcal carriage in European countries or countries with similar epidemiology, using mixed-effects logistic regression to model carriage as a function of age. It estimated carriage at 4.5% for infants, peaking at 23.7% in 19-year olds. Carriage prevalence for New Zealand was based on this.

Figure *33* graphically summarises assumed carriage rates by age as used in this economic evaluation. For information on carriage assumptions by each age, refer to "Attachment 03a_HE Model#3" (Objective ID A1239808).

Figure 33 Carriage prevalence of meningococcal bacterium by age



Source: Christensen et al., Meningococcal carriage by age: a systematic review and meta-analysis. Lancet Infect Dis, 2010. 10(12): p. 853-61

4.2.1.3 Herd Immunity

Herd immunity refers to a form of 'passive' immunity that occurs when the vaccination of a significant proportion of the population provides effective protection for the remaining population who have not been directly vaccinated.

The supplier for Bexsero assumed an indirect effect of herd immunity by the prevention of carriage. The model is dynamic in that the force of infection changes over time based on rates of carriage in the population; while rates of carriage change with the force of infection. By using this structure, the vaccine's protection against carriage acquisition can be estimated, thus incorporating indirect benefits of herd immunity in the unvaccinated population.

To estimate 4CMenB vaccine protection against carriage, the supplier referenced Read et al (2014). The study estimated UK carriage of BCWY capsular groups was reduced by 26.6% from 3 months after the second dose to 12 months after the first dose of 4CMenB vaccine.

The question of herd immunity has been extensively considered by PHARMAC's clinical advice committees and PHARMAC staff. In its 2014 position statement on use of Bexsero® meningococcal B vaccine in the UK, the Joint Committee on Vaccination and Immunisation (JCVI) noted:

"*The Committee noted that an independent analysis of data provided to the Committee by Novartis on the impact of Bexsero® on the acquisition of nasopharyngeal meningococcal carriage in adolescents[21], had been completed[22]. The Committee concluded that the independent evaluation of the Novartis carriage study indicated that the impact of Bexsero® on prevention of acquisition of carriage was likely to be less than 30% but was unlikely to be as low as zero. The Committee agreed that the vaccine probably had a positive impact on carriage in adolescents, but the size of the effect was such that it was not possible to predict accurately what would happen at the population level should the vaccine be used in adolescents. Therefore, the Committee considered that considerable uncertainty remained regarding the cost-effectiveness of a routine adolescent programme in the UK. Impact on acquisition of carriage would have a limited impact on the cost-effectiveness of an infant programme as the impact would be driven by direct protection of the individual rather than herd immunity*."

In March 2019, PHARMAC staff sought advice from the Subcommittee regarding carriage. Minutes from this meeting note:

"*The Subcommittee considered phase 3 randomised clinical trial assessing the effects of meningococcal quadrivalent glycoconjugate (Men ACWY-CRM) or Men B (4CMenB) vaccination on nasal carriage rates in 18-24 year olds (Read et al. Lancet 2014;384:2123-31). The Subcommittee noted that after 12 months Men ACWY-CRM reduced carriage of group Y by 39% and groups CWY by 36.2%. 4CMenB reduce carriage rates of groups BCWY by 26.6%. The Subcommittee considered that the reduction in carriage was lower for group W, so there might be weaker herd immunity effects for W."*

PHARMAC staff discussed this assumption in March 2019 after this meeting. It was subsequently decided the evidence for herd immunity was insufficient to incorporate into economic modelling, with it noted that New Zealand population-wide vaccination would be required to consider using this assumption. Informal sensitivity analysis by PHARMAC staff

indicate that it has minimal impact on final cost-effectiveness. Should further evidence become available in the future, PHARMAC will revisit this assumption.

4.2.1.4 Contact Matrices

The spread of meningococcal is a function of contact between infectious and susceptible individuals. A contact matrix estimates the level of contact between various ages in a given population. This model employs a contact matrix from Mossong et al (2008). This study measured the social structure of approximately 100,000 contacts in 8 European countries (Belgium, Germany, Finland, Great Britain, Italy, Luxembourg, the Netherland and Poland). Participants in these studies were given diaries to record physical and non-physical contacts every day, including details about ages, types of contact, their duration. Mixing patterns were similar across the countries and people of the same age were found to most likely mix with each other.

The resulting contact matrices from these 8 countries have been subsequently used in many infectious disease modelling exercises to predict patterns of outbreak and cost-effectiveness of vaccination. The model employs a matrix that estimates the number of contacts between people of all ages per day and reflects the Great Britain population. For information on the contact matrix, refer to “Attachment 03a_HE Model#3” (Objective ID A1239808).

4.2.2 Review of Supplier Model

PHARMAC staff reviewed and acknowledge the supplier model as conceptually appropriate. PHARMAC staff noted its use and acceptance in the United Kingdom and Australia, including its adaptation from a model for meningococcal C (Trotter et al., 2006).

However, following consideration of expert clinical advice, PHARMAC’s PFPA and New Zealand-specific issues, PHARMAC staff made the following adaptations to the submitted analysis:

- Change the base case infant program from a ‘3+1’ to a ‘2+1’ program. ‘3+1’ refers to infant doses at 6 weeks, 3 months, and 5 months, with a ‘booster dose’ at 12 months; ‘2+1’ refers to doses at 6 weeks and 3 months, with a ‘booster dose’ at 12 months
- Carriage reduction. The supplier assumed the vaccine had efficacy against meningococcal carriage acquisition of 26.6%; following advice from PTAC, this was reduced to 0% (see Section 4.2.1.3 for more details).
- Use of quality of life adjustment factors (QAFs). PHARMAC, in accordance with its methodological approach to pharmacoeconomic analysis outlined in the PFPA, does not practise using QAFs to reflect the severity or seriousness of given conditions or the patient populations in which they occur.
- Removing double-counting of the impact of long-term caregiving. The original supplier model for meningococcal B assumed both a reduction in caregiver utility and a direct cost for caregiving of those patients with long-term sequelae. Methodologically, this is inappropriate; only utility or cost impacts should be captured. PHARMAC modelling subsequently assumed only costs.

Full details of PHARMAC staff review of the supplier model are provided in **Attachment A**. Acknowledging the need for simplicity, reproducibility of outcomes and to facilitate

comparative decision making, PHARMAC staff have prepared their own simplified cost-utility analyses models for the relevant patient groups. This approach is outlined in Section 4.2.3.

4.2.3 Description of Model Structure: PHARMAC developed

As per the PFPA, economic modelling undertaken for assessment purposes by PHARMAC "should avoid unnecessary complexity and should be transparent, well described, and reproducible". However, there will be an inevitable level of complexity associated with modelling meningococcal disease. This is reflected in the considerable number of epidemiological factors influencing disease spread and consequent number of assumptions required to be incorporated in economic modelling to capture all key drivers of outcomes.

PHARMAC staff are also cognisant of the guidance in Section 5.4 of the PFPA regarding vaccine modelling. In particular, consideration should be given to aspects governing vaccine efficacy including vaccine uptake, degree and length of protection, herd immunity.

Further, with PHARMAC's statutory objective to maximise health outcomes for the New Zealander population while operating within a fixed budget, analysis should seek to facilitate comparative decision making amongst potential funding options.

Acknowledging these issues, PHARMAC staff have prepared simplified cost-utility analyses for the relevant patient populations. Cost-utility analyses subsequently developed by PHARMAC staff:

- reflect and adapt key modelling assumptions provided in the original supplier model for meningococcal B;
- reflect the guidance of the PFPA;
- reflect clinical advice received by PHARMAC; and
- reflect the New Zealand clinical and epidemiological environments.

Key elements of PHARMAC modelling developed include:

- instead of a dynamic model, a static model is used. As per clinical advice, no herd immunity is assumed. This means there is no indirect benefit assumed for the broader population in terms of protection or reduced cases. Benefit is assumed to only accrue to the patients directly vaccinated. While the PFPA recommends incorporation of a herd immunity effect if vaccine coverage is expected to be high, PHARMAC have received clinical advice in 2019 (Section 4.2.1.4) that suggests that evidence for such an effect is presently weak at best. As such, to be conservative, PHARMAC modelling only assesses the impact on those directly vaccinated. Should advice be received in the future indicating evidence of herd immunity, PHARMAC should reconsider its modelling approach on this element.
- Instead of a lifetime model capturing new annual cohorts of eligible patients receiving vaccination, with the collective effect impacting the transmission of meningococcal amongst the broader population over time in a dynamic fashion, the static model follows one given cohort of patients vaccinated in the first year of the model.

- For the cohort, assumed rates of uptake, vaccine effectiveness and levels of matching to the given seasonal serogroup strain determine the effective level of direct protection afforded to a given population.
- Members of the population vaccinated in the first year are assumed to have reduced rates of meningococcal cases, hospitalisation, health care resource utilisation, long term sequelae and mortality for the assumed duration of protection.
- Vis-à-vis the non-vaccinated comparator arm, the treatment arm loses less QALYs from acute cases, long term sequelae and mortality and incurs less health care resource utilisation costs during this protection period.
- After the period of assumed protection, members of the vaccinated arm of the model are assumed to then be subject to the same risk of infection for the remainder of their life as the non-vaccinated arm.
- No subsequent vaccination programs are assumed.

Sections 4.3 to 4.8 subsequently outline the inputs used in modelling. Some of these come from the original Bexsero Meningococcal B supplier submission, whilst others are New Zealand specific and have been sourced by PHARMAC staff.

4.3 Event Probabilities

Specified event probabilities are important inputs into the subsequent outcomes generated by the model.

4.3.1 Probability of background mortality

All-cause mortality has been sourced from the Statistics New Zealand publication of New Zealand Period Life Tables: 2012-14. The model incorporates the risk of all-cause mortality from the beginning of the model.

4.3.2 Incident Cases

Incident IMD cases must be considered by overall population incidence, incidence by serogroup and incidence by age. In contrast to other infectious diseases such as influenza, confidence in true incidence of meningococcal cases is high; in 2018, 97.4% of cases were laboratory confirmed (ESR, 2019). As outlined in Section 3.2, incidence of meningococcal strains A, C, W and Y has varied historically in New Zealand. The incidence of meningococcal disease in New Zealand has been predominantly caused by meningococcal serogroups B and C, although W and Y have increased in recent years. Groups W and Y have accounted for more cases than C since 2017. Mortality and morbidity associated with meningococcal C and W is higher than that associated with meningococcal B.

Modelling based on historical incidence requires assumptions to be made about future seasonal severity. PHARMAC staff considered incident elevation in sensitivity analysis based on recent trends and in severe scenarios such as outbreaks.

The base case incidence for the infant and adolescent proposals are based on the most recent incidence data reported by ESR. For high-risk groups such as close contacts of cases and

special immunocompromised individuals, incident rates are sourced from available evidence and reviewed when more accurate and relevant evidence becomes available. Estimated incident rates are outlined in **Table *1010*** below

Table 1010 - Incident rate estimates for Meningococcal B proposals

Meningococcal model B incident rates	**Disease incidence estimate**	**Description**
Infant '2+1' program incidence rate	0.0267%	Sourced from latest ESR data
Entrants to close living situations (13 to 25 years) incidence rate	0.0218%	The latest incidence in age group (13 to 25) sourced from ESR and multiplied by close living environment risk odds-ratio of 10.7 reported by Baker et al. Peer-reviewed in hot-topic.
Entrants for ages 13-25 years in close living situations with CU	0.0218%	The latest incidence in age group (13 to 25) sourced from ESR and multiplied by close living environment risk odds-ratio of 10.7 reported by Baker et al. Peer-reviewed in hot-topic.
Close contacts of confirmed cases incidence rate.	0.0700%	Subsequent attack rate of 0.7 per 1000 household contacts reported by Hoek et al. Peer-reviewed in hot-topic.
Special high-risk immunocompromised groups	0.0439%	Incidence of Men B in HIV patients 43.9 per 100,000 reported by Simmons et al. Peer-reviewed in hot-topic.

The distribution of cases by age is relevant in that it influences the levels of direct effective coverage afforded patients given different vaccination strategies.

4.3.3 Probability of infection

In summary, the probability of infection from all meningococcal serogroups is assumed to be an annual incidence rate of 110/4,924,600 (the New Zealand population as at December 2018 (Stats NZ, 2019), or 0.00203% of the overall population. Sensitivity analysis tests the impact of both higher and lower overall population seasonal incidence levels, accounting for outbreak seasons similar to 2001. For these purposes, it is assumed the proportion of cases by age is unchanged.

Of these, 45% are assumed to be of serogroup B, translating into an annual population wide probability of infection of approximately 0.001%.

Age-specific rates are can be viewed in document “Attachment 03a_HE Model” (Objective ID A1118195).

For those in high risk populations, risk is assumed to be elevated. There is limited data on the precise elevation in relative risk for these groups (boarding schools, tertiary residences, armed forces living quarters and prisons), however it is assumed that those in close-living sub-populations and those immunocompromised high-risk patients having the highest rates of risk. This is affected in the model by proportionately adjusting the assumed incidence rates for the relevant sub-populations.

4.3.4 Probability of hospitalisation

It is assumed all cases are hospitalised, regardless of age or meningococcal serogroup. In addition, it is assumed a specified percentage spend time in ICU. Bettinger et al (2013) found approximately 60% of adults and 61% of children spent time in ICU. PHARMAC staff reviewed these assumptions and deemed them reasonable.

4.3.4.1 Probability of mortality

June 2020 – update
In 2019 there was a total of 5 deaths from meningococcal B increasing the CFR rate from 5% in 2018 to 6.1% in 2019. The CFR rate is calculated from total incident cases in the last 6 years and total deaths in the last 6 years. Between 2014 and 2019 there were a total of 297 Men B cases and 18 deaths – 18/297= 6.1%The increased CFR rate impacts the CUA ranges for the infant (2 + 1) proposal which is sensitive to CFR rate.

The assumed CFR is a key driver of model outcomes. Literature suggests upwards of 10% of patients will die. Historical New Zealand for meningococcal B fatalities during the period 2007 to 2016 indicate a low proportion of fatalities, with an average of 4.3% across the entire population.

For the purposes of analysis and to be consistent with assumed average annual cases numbers and distribution by serogroup, it is assumed the CFR is approximately 4.3%, applicable across all age ranges. This is tested in sensitivity analysis.

4.3.5 Probability of long-term sequelae

Long-term sequelae are an important consequence, affecting health care costs and patient quality of life. As previously outlined in section 3.1, serogroups A, C, W and Y have experienced higher rates of sequelae than serogroup B. The supplier submission for Bexsero assumed the following material long-term sequelae and rates, based on its analysis of observational studies and a literature review of health economics studies. PHARMAC staff view these as broadly appropriate.

Table 1111 Meningococcal sequelae rates for group B

Long Term Sequelae	Group B Rate (%)
Hearing Loss	11.46%

Severe neurological sequelae	6.62%
Amputation with severe disability	1.26%
Epilepsy and seizure	1.78%
Skin scarring	6.39%
Renal failure	2.05%
Blindness	0.42%
ADHD/Anxiety	17.87%

Source: Supplier application, Bexsero, January 2018 (Objective ID A1239808).

4.3.6 Meningococcal Outbreak

Disease outbreaks are localised increases in the occurrence of disease clearly more than normally expected levels (ESR, 2019). Responses to outbreaks have the primary purpose of quickly administering an immunisation programme to interrupt the chain of community transmission. The most recent meningococcal serogroup outbreak was in Northland DHB in November 2018 for meningococcal W.

PHARMAC staff considered that following the historical outbreak period between 1991 and 2007, and the subsequent significant reduction in annual case numbers since peak incidence of meningococcal cases in 2001, that risk of a meningococcal B based outbreak i of a low level of probability. As such, it is not included in the comparator arm of the model.

4.4 Population Cohorts and Births

Patient numbers for each proposal are a function of the number of New Zealand people in each age cohort and projected births. These numbers are sourced from Stats New Zealand.

It should be noted that annual birth rates in New Zealand have historically varied. Analysis of the last 10 years of births puts the estimated average annual births at approximately 60,000. In practice, births may differ from this and this should be acknowledged.

4.5 Coverage

Both cost-effectiveness and budget impact outcomes are sensitive to assumptions regarding vaccination uptake. Coverage is likely to vary by vaccine sub-population. Uptake reflects feedback from the Immunisation Sub-committee in May 2018 and March 2019 on the specified sub-populations:

- 75% in closed living situations for adolescents and young adults (i.e. aged 13 to 25 in university residences, prisons, armed forces barracks and private dorms); and
- 90% for infants. NIS full coverage targets for infants/children are typically 95%, but data from Ministry of Health as at March 2018 shows this has not quite been achieved (12-month completion is estimated at 93.6%, 24-months at 92%).

PHARMAC staff have assumed immunocompromised patients and close contacts of cases and prior cases have a 100% uptake.

4.6 Patient population definitions and sizes

Patient population definitions affect cost-effectiveness and budget impact. Patient populations, including numbers for the first five years of any listing, are summarised in **Table 1313**. These reflect assumptions about uptake, New Zealand population cohort and projected birth numbers, as well as specific analysis defining close-living sub-populations.

4.6.1 Close-living Sub-Populations

These sub-populations are defined as those between the ages of 13 and 25 living in boarding school dormitories, tertiary education residences, prisons and armed forces living quarters.

Table 1212 summarises these populations. Full details on their calculation are in document "Budget Impact Analysis work up for Meningococcal" (Objective ID A1255755). PHARMAC staff should consider confirming these prior to any actual vaccination program.

Table 1212 Estimated Relevant Close Living Sub-Populations

Patient Sub-population	Total
Prisoners (sentenced) aged 25 and under	1,013
Armed forces (barracks/living quarters) 25 and under	4,677
Tertiary education residential students (dormitories, residential living blocks)	16,000
Boarding school students (dormitories)	13,500
Total	**35,190**

Sources: New Zealand Defence Force (/www.nzdf.mil.nz/downloads/pdf/public-docs/2017/2016-2017-nzdf-annual-report.pdf); New Zealand Department of Corrections (Department of Corrections New Zealand, 2017 (http://www.corrections.govt.nz/resources/research_and_statistics/quarterly_prison_statistics.html); Education Counts (NZ Ministry of Health, www.educationcounts.govt.nz/statistics/tertiary-education/participation, www.educationcounts.govt.nz/statistics/schooling/student-numbers/6028, www.educationcounts.govt.nz/find-school).
Notes: Estimated boarding/close-living populations sourced from going to websites of the individual education providers listed in data tables provided by 'Education Counts'. Some listed boarding schools at 'Education Counts' did not specify boarding student population numbers; imputed values have been used based on average numbers of boarding schools with specified boarding populations (approximately 65% of the 96 listed schools had boarding student numbers published). Tertiary education residential student numbers are based on publicly available information referencing listed tertiary education providers from 'Education Counts' but may be higher.

Table 1313 Estimated Patient Numbers by Sub-Population

	Year 1	Year 2	Year 3	Year 4	Year 5	5-year total
1 dose at age 12 months	54,000	54,000	54,000	54,000	54,000	270,000
1 dose at 12 months plus catch	6,092	6,092	6,092	6,092	6,092	30,458

up for ages 1-4 years first year only						
1 dose adolescents at 12 years of age	26,392	6,092	6,092	6,092	6,092	50,759
1 dose catch up for ages 5-21 years for 1 year only	1,900	1,100	1,100	1,100	1,100	6,300
1 dose catch up for ages 13-21 years for 1 year only	300	300	300	300	300	1,500

Source: “Meningococcal B_MARCH_2020_CUA_BIA” (Objective ID A1345969)

4.7 Efficacy

September 2020 – update

For the adolescent proposals, entrants to close living environments (13 to 25 years) no catch up, entrants to close living environments (13 to 25 years) plus catch up. The duration of vaccine efficacy has been increased from 5-years to 7 years. This is informed by new evidence provided by the supplier (Nolan et al, 2018) and recommended in hot-topic to be included in the base case.

The supplier cited a 3-year surveillance study of the safety and effectiveness of the UK 4CMenB infant vaccination programme in England. The initial target of the vaccination programme was 700,000 infants. By January 2016, approximately 94% of the target population had received one dose of 4CMenB and 85% had received two doses. In the first 10 months of implementation, a reduced two-dose infant priming schedule was 82.9% effective in preventing disease in infants aged younger than 12 months. For the purposes of assessment, it is assumed that patients receive three years of protection, with a mean effectiveness of 82.9% assumed (Al-Janabi et al., 2016). With limited data for all patient groups, this rate of efficacy is assumed for all populations.

Patient coverage is ultimately a function of vaccine effectiveness and serogroup strain matching. MATS tests are used to determine the level of ' strain matching' of a vaccine with existing strains of a serogroup. A vaccine with strong strain matching is likely to be more effective and offer better population coverage from circulating meningococcal B strains meningococcal B in the community.

For Bexsero vaccine for meningococcal B, the supplier used the MATS assay to predict strain coverage. Patient coverage is ultimately a function of vaccine effectiveness and serogroup strain matching. MATS tests are used to determine the level of 'matching' of a vaccine with existing strains of a serogroup. MATS results from nine European countries, Australia, USA, Brazil and Canada covering nearly 2,700 meningococcal B strains estimated that 66–91% of strains would be covered by 4CMenB. In Australia, it was estimated that 76% strain coverage would occur; in the UK this rate is 66% in 2014-15. MATS testing is not available in New Zealand and therefore Australian matching data has been used in the health economics model.

4.8 Health-Related Quality of Life

Values used in the model are summarised in **Table 1414**.

Table 1414 Utility values associated with long-term sequelae

Long Term Sequelae	Utility Value
Hearing Loss	0.89
Severe neurological sequelae	0.71
Amputation with severe disability	0.69
Epilepsy or seizure	0.83
Skin scarring	1.00

Renal failure	0.82
Blindness	0.26
ADHD/Anxiety	0.75

Source: "Attachment 03a_HE Model#3" (Objective ID A1239808)

Quality of life losses for the patents with acute IMD and for survivors with long-term sequelae are based on the supplier submission for Bexsero (Objective ID A1117983). Utility decrements of 0.201 were applied to acute IMD cases. Utility decrements of 0.19 were applied to IMD cases with sequelae, based on the UK cost-effectiveness analysis of 4CMenB vaccination in the UK by Christensen et al (2014). Based on the eight defined categories of long-term sequelae previously defined in section 4.3.5, the supplier undertook a systematic literature review for HRQoL values. PHARMAC staff reviewed all utility values and deemed them reasonably appropriate, albeit in some cases perhaps underestimating actual quality of life impacts (i.e., for severe long term sequelae). Analysis reflects this.

4.9 Costs

4.9.1 Vaccination costs

In December 2019, the supplier proposed a revised net price of s9(2) per dose for infant and adolescent proposals and s9(2)(b) per dose for the smaller immunocompromised and close contact proposals. All infants receive three doses, all patients in all other populations receive two.

4.9.2 Adverse Event Costs

Minor adverse events costs are included. Higher rates of fever have been observed in infant patients taking Bexsero concurrently with other vaccines. It should be noted that prophylactic intervention (e.g. paracetamol) is low cost and fever has minimal impact on patient quality of life.

4.9.3 Administration Costs

For patient populations where there are no lines currently listed on the NIS, additional administration costs are assumed. For vaccine administration, the immunisation subsidy is the amount a GP surgery receives for administering a vaccine to an eligible patient and is $20.51 (internal PHARMAC document "2018 Cost Spreadsheet for CUAs" (original source https://www.health.govt.nz/our-work/primary-health-care/primary-health-care-subsidies-and-services/capitation-rates)).

4.9.4 Disease Management Costs

Disease management costs relate to case identification, outbreak management costs (treatment), acute IMD cases (i.e., hospitalisation) and long-term sequelae. From the supplier submission for Bexsero, PHARMAC staff note the following cost categories and amounts assumed for acute and long-term management of IMD patients. These cost categories align with the sequelae categories identified earlier in this TAR. PHARMAC staff have reviewed these amounts, including their calculation, viewing them to be broadly appropriate.

Table 1515 Acute Care and Long-term sequelae disease management costs

Cost Item	Amount ($)
Case identification and confirmation (per patient)	$443
Outbreak costs (per patient treatment)	$100
Acute Care Costs (hospitalisation) (ages 0 to 17)	$23,245
Acute Care costs (hospitalisation) (ages 18+)	$30,535
Hearing loss (first year)	$12,475
Hearing loss (subsequent years)	$2,221
Severe neurological sequelae (first year)	$5,192
Severe neurological sequelae (subsequent years)	$946
Amputation with severe disability (first year)	$23,503
Amputation with severe disability (subsequent years)	$2,517
Epilepsy/seizure (first year)	$3,943
Epilepsy/seizure (subsequent years)	$731
Skin scarring (first year)	$2,400
Skin scarring (subsequent years)	$0
Renal failure (first year)	$2,788
Renal failure (subsequent years)	$413
Blindness (first year)	$7,628
Blindness (subsequent years)	$7,628
ADHD/Anxiety (first year)	$996
ADHD/Anxiety (subsequent years)	$996

Source: “Attachment 03a_HE Model#3” (Objective ID A1239808)

5 Results of Economic Analysis

5.1 Base Case Results

June 2020 update –

Due to the increased incidence in infants and CFR rate for 2019 the CUA ranges for the infant (2 + 1) proposal have increased. Previously the likely and possible ranges on the OFI for the infant 2 + 1 proposal were s9(2)(b) and s9(2)(b), respectively. These ranges have s9(2)(b)(ii), s9(2) s9(2)(b) in the likely range.

Indicative base case cost effectiveness results for each sub-population are presented in **Table *1616***. PHARMAC staff would note that base case results are based on potentially favourable assumptions for key inputs (e.g. duration of vaccine protection). PHARMAC staff recommend the analysis be re-visited should additional data or evidence become available.

Table 1616 Indicative Base Case Results: Cost per QALY and QALYs per $1m for Vaccination vs. No Vaccination

Population groups	Likely QALYs per $m range
Infant '2+1' program.	s9(2)(b)
Entrants to close living situations (13 to 25 years).	s9(2)(b)
Entrants catch up for ages 13-25 years in close living situations for 1 year only and ongoing entrants as above.	s9(2)(b)
Special high-risk immunocompromised groups - same as ACWY high risk criteria).	s9(2)(b)
Close contacts of confirmed cases.	s9(2)(b)

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969). **Note* CUA results for immunocompromised groups and close contact proposals are reflective of a higher price s9(2) The infant and adolescent proposals are reflective of a commercial price offer of approx s9(2 per dose.**

5.2 International Comparison

PHARMAC staff note assessments by international agencies. PHARMAC staff considered the commentary of the UK's JCVI in 2014, particularly its conclusions regarding its deliberations on the cost-effectiveness of using serogroup B meningococcal (MenB) vaccine in the UK, both routinely in infants and in at-risk groups.

The JCVI makes its decisions on vaccines separately from the National Institute for Health and Care Excellence (NICE), which looks at other medicines, and operates a slightly different health economic rating. Its current cost-effectiveness threshold is set at £20,000 per QALY. It is also noted that in comparison, NICE has a general cost per QALY threshold for acceptability of decisions of approximately £30,000 per QALY.

Following iterations of analysis performed independently, based on specific JCVI feedback, it concluded, "*The consensus of the Committee was that whilst uncertainty remained, and whilst in some scenarios the vaccine would not be cost-effective at a positive vaccine price, the results of the final iteration of the cost-effectiveness model indicated that for an infant*

programme, in the scenarios considered most plausible by the Committee, the vaccine was still cost effective (at a very low positive price)."

The JCVI did not publicly disclose what such a price would be deemed 'cost-effective'. It should be noted that final analysis incorporated revisions suggested by the JCVI including:

- Inclusion in the base case model of a quality of life adjustment factor (QAF) of 3 agreed by the JCVI in June 2013 (as opposed to this being accounted for in an additional sensitivity analysis as had been done previously);
- Inclusion of a proportion of litigation costs associated with meningococcal disease in the NHS; and
- Inclusion of quality of life losses to family members.

It should be noted that none of these economic evaluation practices are in accordance with the recommendations of PHARMACs PFPA for base case economic evaluation. PHARMAC staff in particular tested the impact of using a QAF in the supplier model and noted that by itself it considerably improved the cost-effectiveness of final outcomes.

PHARMAC staff also noted the Pharmaceutical Benefits Advisory Committee (PBAC) findings in Australia. In November 2013, a major submission requested the inclusion of 4CMenB in the Australian National Immunisation Program (NIP) with a proposed vaccination schedule of 3+1 in infants, a two-dose course in adolescents and a catch-up programme in older infants, toddlers and adolescents. The submission presented an incremental cost per QALY between AU$45,000 and AU$75,000 per QALY (i.e., 13 to 22 QALYs per $1m). The PBAC expressed several concerns including:

- lack of direct evidence of vaccine efficacy against infection and disease
- lack of evidence demonstrating ability of vaccine to generate a population level protective herd immune response
- increasing uncertainty in predicting efficacy based on MATS estimated coverage due to heterogeneity of antibody responses and waning of antigen-specific titres over time
- an unacceptably high ICER that was based on uncertain assumptions about the extent and duration of effect and herd immunity

A minor re-submission was sought in July 2015 that presented a cost-utility model with a revised base case resulting in cost per QALY outcomes ranging from of AU$45,000–AU$200,000 per QALY for the vaccination schedules compared to no vaccination, a 'preferred strategy' yielding a cost-effectiveness range between AU$105,000 and AU$200,000 (i.e., approximately 5 to 10 QALYs per $m).

PHARMAC staff note that in its March 2018 consideration of meningococcal polysaccharide conjugate vaccine serogroups A, C, W-135 and Y (Nimenrix), the Australian PBAC recalled that for vaccination programs a cost per quality adjusted life year (QALY) of $15,000 or less is generally considered acceptable and that the vaccine price for the application in question should be reduced to ensure cost-effectiveness satisfied this threshold criteria.

PHARMAC's decision making does not reflect explicit cost-effectiveness threshold criteria. Nonetheless, international agency comparisons are useful references.

5.3 Limitations and Interpretation

Results are subject to several limitations and caveats in interpretation. Modelling infectious diseases in a population is highly complex. Whilst economic modelling undertaken for assessment purposes by PHARMAC "should avoid unnecessary complexity and should be transparent, well described, and reproducible" (PHARMAC PFPA), there will be an inevitable level of complexity associated with modelling meningococcal disease.

There are a considerable number of epidemiological factors influencing disease spread and the consequent number of assumptions required to be incorporated in economic modelling to capture all key drivers of outcomes across all patient populations. In addition, there can be difficulty in accurately or consistently predicting the interactive effects of all key factors on ultimate outcomes in practice.

Even with the simplified cost-utility analyses undertaken by PHARMAC, this still sees a significant number of inputs and assumptions employed. As such, final cost-effectiveness results are presented as ranges for the respective population groups. PHARMAC staff should consider revisiting analysis should assumptions or inputs (e.g. herd immunity) change over time.

The use of a static model instead of a transmission dynamic model aims for simplicity, reproducibility and comparability of outcomes between patient populations to facilitate decision making. Whilst static modelling may not trace the flow of infection across the time duration of the model as a function of numerous interactive factors, PHARMAC staff believes it to provide for a reasonable measure of disease cases, health outcomes and associated costs by measuring the direct impact on vaccinated patients. This is particularly the case given no herd immunity is assumed and there is current uncertainty regarding the level and duration of direct protection afforded vaccinated patients.

Even with dynamic models, there can be difficulty in accurately or consistently predicting the interactive effects of all key factors on end results. Further, for smaller sub-populations, the value of some of these input assumptions are uncertain or there is limited evidence for them. For example, immunocompromised patients are at an elevated risk of infection (van Keen et al., 2016) but there is limited evidence for the relative risk and the associated effectiveness of vaccines in immunocompromised patients (Arora, 2019) for meningococcal.

As such, it should be noted cost-effectiveness results for smaller sub-populations are based on limited evidence and assessments for these have been undertaken primarily to establish relative cost-effectiveness of sub-populations. The results should be used as a guide of which groups may be more cost-effective than others, rather than precise absolute estimates.

PHARMAC staff note there is no direct evidence from randomised controlled trials that 4CMenB vaccination reduces rates of IMD (Supplier submission, Objective ID A1117983). Effective patient coverage is ultimately a function of vaccine effectiveness and serogroup strain matching. Treatment effectiveness is based on a 3-year surveillance study of the safety and effectiveness of the UK 4CMenB infant vaccination programme in England, with it assumed patients receive three years of protection (Parikh et al, 2016), with a mean effectiveness of 82.9% assumed (Al-Janabi et al., 2016). PHARMAC staff should consider revisiting analysis should new evidence become available.

Cost-effectiveness results are presented as single ranges, but this reflects that cost-effectiveness of the same vaccination program would change over time. The 'point-in-time' cost effectiveness will likely change as a program unfolds. An effective vaccination program that reduces incident cases means there is a reduced number of infected individuals in the population and therefore a smaller 'pool' of patients from which the disease can continue to spread. The subsequent annual vaccination of additional 'new' population cohorts every year reduces the susceptibility of the population to infection. Over time, this would likely result in the prevention of fewer and fewer cases meaning so each year is less cost-effective.

Meningococcal disease is seasonal in nature and severity and as such cost-effectiveness is dependent on the seasonal incidence in given patient sub-populations. Unlike other diseases which generally have established epidemiology, infectious diseases can be unpredictable, meaning cost-effectiveness can vary over time. Therefore, cost-effectiveness is assessed based on an assumed average seasonal incidence rate that would occur without the rollout of a vaccination program, reflecting recent historical data. It should be noted however that such a 'background' incidence rate may not occur in the future and thus timing of any vaccination program will influence its cost effectiveness.

The changing balance in dominating meningococcal serogroups should also be noted. Historically, the B serogroup has dominated, but in recent years has become a smaller proportion of cases. The growing incidence and severity of the W strain, as reflected in the case fatality ratio (CFR) experienced in New Zealand in 2017 and 2018 and its' growing proportion of meningococcal cases in Australia has been acknowledged, along with the potential for a higher proportion of cases experiencing long term sequelae. It should also be noted that in 2017 and 2018 in New Zealand, a high proportion of cases have been seen for the Y strain, with a decline in C serogroup cases. Further, of the cases across these serogroups, a high percentage have been in patients greater than 20 years of age. This demographic distribution may change over time and hence also subsequently affect cost-effectiveness (and budget impact).

Budget impact is influenced by both trends in uptake and vaccine pricing. Demand for vaccines worldwide is currently high, shaping available stock and pricing dynamics. Rates of uptake will change the budget impact of any given program. Both of these in turn will also influence any program's cost-effectiveness.

5.4 Sensitivity Analysis

To test the robustness of the base case outcomes, inputs have been analysed univariately. Given the considerable number of input assumptions required to model meningococcal disease and the multiple patient populations considered by this TAR, only those with material effect are detailed. Cost-effectiveness results are sensitive to price, assumed annual seasonal incidence, the CFR and proportion of patients experiencing long-term sequelae.

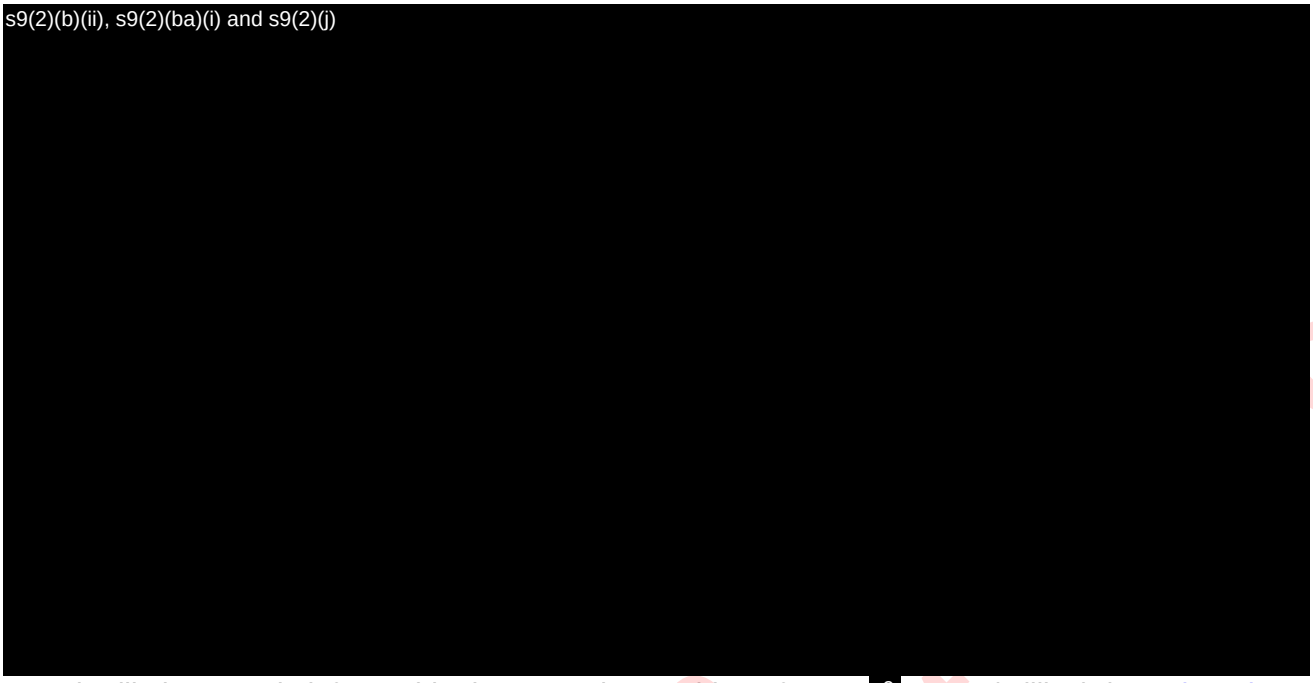
For full details of sensitivity analysis results, refer to "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969).

Table 1717 Summary: Sensitivity Analysis by Population Group

Variable	Value	Infant '2+1' Program	Entrants to close living situations 13 to 25 years	Entrants to close living situations 13 to 25 years and year 1 catch up	Close contacts confirmed cases	Special high-risk immunocompromised groups - same as ACWY high-risk criteria.	Parameter description
Base case		s9(2)	s9(2	s9(2)	s9	s9(	
Incidence	+ 50% 2019 incidence	s9(	s9(	s9(	s9	s9(	Current estimated incidence increased by 50%. During the 2001 outbreak incidence rates increased to 4.5 times the amount they are now. A 50% increase is to represent if incident rates continue to increase from low levels in 2016 and if New Zealand was in the early stages of an outbreak.
	Double 2019 incidence	s9(2	s9(	s9(	s9(	s9(	Current estimated incidence increased by 100%. During the 2001 outbreak incidence rates increased to 4.5 times the amount they are now. A 100% increase is to represent if incident rates were to significantly increase and New Zealand was in the early stages of an outbreak
Uptake - % uptake within patient population	50%	s9(	s9(	s9(	s9(	s9(	Low level of vaccine uptake
	100%	s9	s9	s9(2	s9	s9	High level of vaccine uptake
Efficacy Duration (years)	5 to 6	s9(	s9(	s9(	s9(	s9(	Vaccine efficacy duration is increased from 4 to 6 years for infants, close contacts and special high-risk immunocompromised and vaccine efficacy is decreased from 7 years to 5 years for adolescents
Efficacy %	71%	s9(	s9(2	s9(	s9	s9(	Decreased vaccine efficacy Parikh et al. 2016
Efficacy %	94%	s9(	s9(	s9(	s9	s9(	Increased vaccine efficacy Parikh et al. 2016
MATS %	61%	s9(	s9	s9(	s9(	s9	Decreased strain matching; Muzzi et al 2019
MATS %	86%	s9	s9(	s9(2	s9(	s	Increased strain matching; Muzzi et al 2019
% mortality	4.1%	s9	s9(	s9(	s9	s9(	CFR of 1996 to 2001 outbreak
% mortality	8.3%	s9(	s9	s9(	s9	s9(	CFR of meningococcal b strain P(1.7, 2,4)

% long term sequelae rate	10%	s9(	s9	s9(	s9	s9(	Deceased sequelae rate; Olbrich et al
% long term sequelae rate	20%	s9(	s9(	s9(	s9	s9(	Increased sequelae rate; Olbrich et al

Graph 11 Infants - sensitivity analysis (QALYs per $m)



The likely range is informed by lower strain matching of 66% (s9 QALYs/million) (Muzzi et al. 2019 Feb 8;37(7):991-1000) and if incidence increased by a further 50% (s9(QALYs/million). Within the likely range of s9(to s9(additional parameters tested include, a 100% uptake rate, if vaccine efficacy increased to 94% (Parikh et al. 2016 Dec 3;388(10061):2775-2782), if the rate of long-term sequelae increased to 20% and if strain matching increased to 91%(Muzzi et al. 2019 Feb 8;37(7):991-1000).

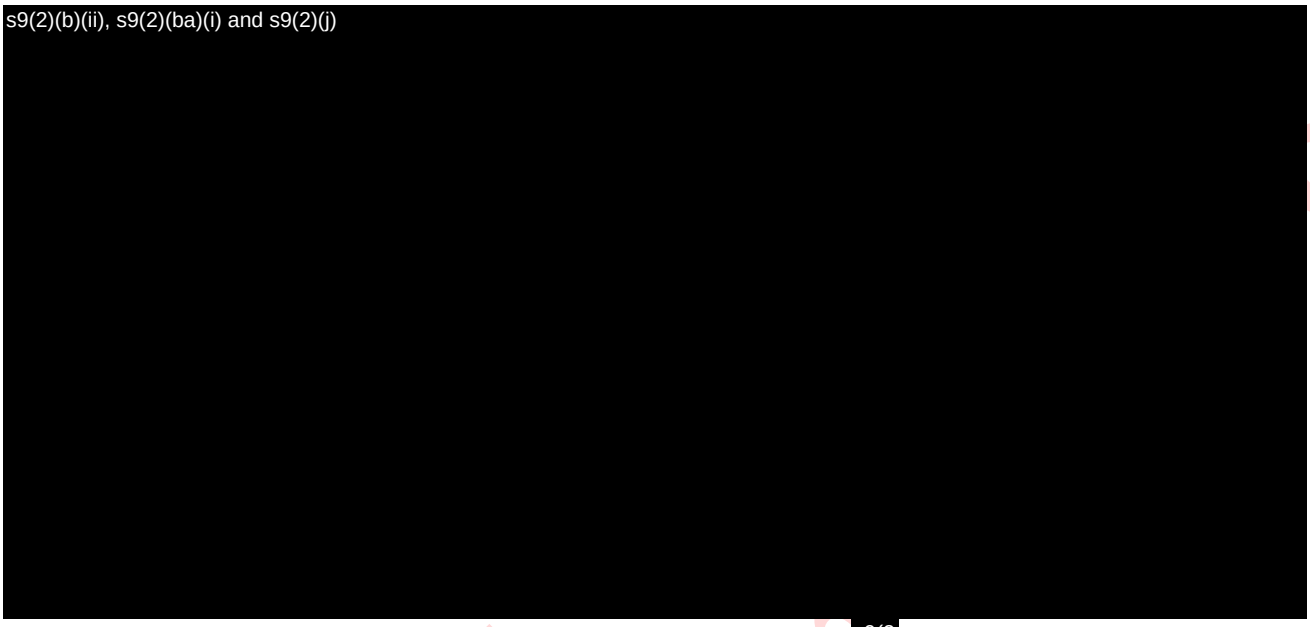
The possible range is informed by the CFR rate decreasingto 4.1% (s QALYs/million) and the incidence rates doubling (s9(QALYs/million). Within the possible range of s to s9(additional parameters tested include, a higher mortality rate of 8.3%, decreased uptake (50%), increased vaccine efficacy duration to 6 years, a lower rate of long-term sequelae and if vaccine efficacy reduced to 71%. Sources and justification for parameters are outlined in **Table *1717***.

Graph 22 Adolescents (13 to 25 years) - sensitivity analysis (QALYs per $m)

The likely range is informed by lower strain matching of 66% (s9(QALYs/million) (Muzzi et al. 2019 Feb 8;37(7):991-1000) and if incidence increased by a further 50% s9(QALYs/million). Within the likely range of s9(2)(b)(ii), , additional parameters tested include, a 100% uptake rate, if vaccine efficacy increased to 94% (Parikh et al. 2016 Dec 3;388(10061):2775-2782), if the rate of long-term sequelae increased to 20% and if strain matching increased to 91%(Muzzi et al. 2019 Feb 8;37(7):991-1000).

The possible range is informed by a CFR rate decreasing to 4.1% s9 QALYs/million) and incidence rates doubling s9(QALYs/million). Within the possible range of s9(2)(b) , additional parameters tested include, a higher mortality rate of 8.3%, decreased uptake (50%), reduced vaccine efficacy duration to 5 years, a lower rate of long-term sequelae and if vaccine efficacy reduced to 71%. Sources and justification for parameters are outlined in **Table *1717***.

Graph 33 Special high-risk immunocompromised - sensitivity analysis (QALYs per $m)



The likely range is informed by lower strain matching of 66% (s9(2 QALYs/million) (Muzzi et al. 2019 Feb 8;37(7):991-1000) and if incidence increased by a further 50% (s9(QALYs/million). Within the likely range of s9(2)(b)(ii), additional parameters tested include, a 100% uptake rate, if vaccine efficacy increased to 94% (Parikh et al. 2016 Dec 3;388(10061):2775-2782), if the rate of long-term sequelae increased to 20% and if strain matching increased to 91%(Muzzi et al. 2019 Feb 8;37(7):991-1000).

The possible range is informed by, a decreased CFR rate of 4.1% (s9(QALYs/million) and if incidence rates were doubled (s9(QALYs/million). Within the possible range of s9(2)(b)(ii), additional parameters tested include, a higher mortality rate of 8.3%, decreased uptake (50%), increased vaccine efficacy duration to 6 years, a lower rate of long-term sequelae and if vaccine efficacy reduced to 71%. Sources and justification for parameters are outlined in **Table *1717***.

Graph 44 Close contacts of cases - sensitivity analysis (QALYs per $m)

The likely range is informed by lower strain matching of 66% (s9(QALYs/million) (Muzzi et al. 2019 Feb 8;37(7):991-1000) and if incidence increased by a further 50% (s9(QALYs/million). Within the likely range of s9(to s9(additional parameters tested include, a 100% uptake rate, if vaccine efficacy increased to 94% (Parikh et al. 2016 Dec 3;388(10061):2775-2782), if the rate of long-term sequelae increased to 20% and if strain matching increased to 91%(Muzzi et al. 2019 Feb 8;37(7):991-1000).

The possible range is informed by, a decreased CFR rate of 4.1% (s9(QALYs/million) and if incidence rates were doubled (s9(QALYs/million). Within the possible range of s9(to s9(additional parameters tested include, a higher mortality rate of 8.3%, decreased uptake (50%), increased vaccine efficacy duration to s9 years, a lower rate of long-term sequelae and if vaccine efficacy reduced to 71%. Sources and justification for parameters are outlined in **Table *1717***.

6 Budget Impact Analysis

Budget impact analysis assesses two categories of costs associated with any Bexsero vaccination program:

1. Costs of adding the Bexsero vaccination to the NIS. This includes vaccine and administration costs.
2. Cost savings associated with reduced cases of IMD, including acute care and long-term sequelae costs.

6.1 Vaccination Program Budget Impact

6.1.1 Infant '2+1' program

Table 1818 summarises the estimated yearly and 5-year NPV CPB and DHB budget impacts. Over five years the estimated NPV DHB impact would be approximately s9(2)(b) (s9(2)(b)(ii), CPB).

Table 1818 Estimated CPB and DHB impact of immunising infants

Item	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Eligible Population	60,000	60,000	60,000	60,000	60,000	300,000
Uptake rate (%)	90%	90%	90%	90%	90%	
Patient Population	54,000	54,000	54,000	54,000	54,000	270,000
Dosing	2	3	3	3	3	
Unit Price	s9(2)(b)	s9(2)(b)	s9(2)(b)	s9(2)(b)	s9(2)(b)	
Total Vaccine Budget Impact	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Administration Unit Cost		$20.51	$20.51	$20.51	$20.51	
Total direct cost due to disease saved	-$171,018.00	-$302,513.00	-$376,368.00	-$433,823.00	-$520,465.00	**-$1,500,738**
Total Administration Budget Impact		**$1,107,540**	**$1,107,540**	**$1,107,540**	**$1,107,540**	**$3,668,313**
Total other health care cost	**-$171,018.00**	**$805,027.00**	**$731,172.00**	**$673,717.00**	**$587,075.00**	**$2,170,000**
Total Vaccine Program Costs	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969)
Notes: Individual year amounts undiscounted. Dosing in the first year is 2 doses, reflecting the booster dose for the first cohort of patients being in the following year. Subsequently each financial year of analysis indicates patients receiving on average 3 doses.

6.1.2 Entrants to close living situations (13 to 25 years)

Table 1919 summarises the estimated yearly and 5-year NPV CPB and DHB budget impacts. Over five years the estimated NPV DHB impact would be approximately s9(2) (s9(2)(b) CPB).

Table 1919 Estimated CPB and DHB impact of immunising entrants to close living situations (13 to 25 years)

Item	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Eligible Population overall	8,122	8,122	8,122	8,122	8,122	40,610

Eligible Population overall (13 to 18)	6,868	6,869	6,870	6,871	6,872	34,350
Eligible Population overall (19 to 25)	1,254	1,254	1,254	1,254	1,254	6,270
Uptake rate (%)	75%	75%	75%	75%	75%	
Patient Population	6,092	6,092	6,092	6,092	6,092	30,458
Dosing	2	2	2	2	2	
Unit Price	s9(2)(b)(ii),	s9(2)(b)	s9(2)(b)	s9(2)(b)	s9(2)(b)	
Total Vaccine Budget Impact	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Administration Unit Cost	$20.51	$20.51	$20.51	$20.51	$20.51	
Total direct cost due to disease saved	-$25,722.37	-$45,500.20	-$56,608.54	-$65,250.19	-$78,281.79	**-$225,722**
Total Administration Budget Impact	**$249,873**	**$249,873.33**	**$249,873**	**$249,873**	**$249,873**	**$1,077,485**
Total other health care cost	**$224,151**	**$204,373**	**$193,265**	**$184,623**	**$171,592**	**$850,000**
Total Vaccine Program Costs	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969)
Notes: Individual year amounts undiscounted.
After initial catch-up program, subsequent years vaccination relates to annual cohort of patients aged 12 months.

6.1.3 Catch up for ages 13-25 years in close living situations for 1 year only and ongoing entrants

Table *2020* summarises the estimated yearly and 5-year NPV CPB and DHB budget impacts. Over five years the estimated NPV DHB impact would be approximately s9(2)(b)(ii), s9(2)(ba)(i) and

Table 2020 Estimated CPB and DHB impacts of immunising catch up for ages 13-25 years in close living situations for 1 year only and ongoing entrants

Item	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Eligible Population overall	27,067	8,122	8,122	8,122	8,122	59,555
Uptake rate (%)	75%	75%	75%	75%	75%	
Patient Population (catchup)	20,300					20,300
Patient Population (entrants)	6,092	6,092	6,092	6,092	6,092	30,458
Patient Population total	26,392	6,092	6,092	6,092	6,092	50,758

Dosing	2	2	2	2	2	
Unit Price	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)	s9(2)(b)	s9(2)(b)	
Total Vaccine Budget Impact (1 year catch up)	s9(2)(b)(ii),					s9(2)(b)(ii),
Total Vaccine Budget Impact (entrants)	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Total VaccineBudget Impact	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Administration Unit Cost	$20.51	$20.51	$20.51	$20.51	$20.51	
Total direct cost due to disease saved	-$83,583	-$34,125	-$42,456	-$48,938	-$58,711	**-$233,582**
Total Administration Budget Impact	**$1,082,590**	**$249,873**	**$249,873**	**$249,873**	**$249,873**	**$1,910,202**
Total other health care cost	**$999,007**	**$215,748**	**$207,417**	**$200,936**	**$191,162**	**$1,680,000**
Total Vaccine Program Costs	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969)
Notes: Individual year amounts undiscounted.

6.1.4 Special high-risk immunocompromised groups - same as ACWY high risk criteria)

Table 2121 summarises the estimated yearly and 5-year NPV CPB and DHB budget impacts. Over five years the estimated NPV DHB impact would be approximately s9(2)(b)(ii), s9(2)(ba)(i) and

Table 2121 Special high-risk immunocompromised groups - same as ACWY high risk criteria)

Item	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Eligible Population (catch up)	800					800
Eligible Population (incident)	1,100	1,100	1,100	1,100	1,100	5,500
Uptake rate (%)	100%	100%	100%	100%	100%	
Patient Population	1,900	1,100	1,100	1,100	1,100	6,300
Dosing	2	2	2	2	2	
Unit Price	s9(2)(b)	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)	
Total Vaccine Budget Impact	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Administration Unit Cost	$20.51	$20.51	$20.51	$20.51	$20.51	
Total direct cost due to disease saved	-$6,017	-$6,162	-$7,667	-$8,837	-$10,602	**-$33,104**

Total Administration Budget Impact	**$77,938**	**$45,122**	**$45,122**	**$45,122**	**$45,122**	**$227,388**
Total other health care cost	**$71,921**	**$38,960**	**$37,455**	**$36,285**	**$34,520**	**$194,000**
Total Vaccine Program Costs	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969)

Notes: Individual year amounts undiscounted. Note there is assumed to be a prevalent pool of patients who would immediately take the vaccine.

6.1.5 Close contacts of confirmed cases

Table 2222 summarises the estimated yearly and 5-year NPV CPB and DHB budget impacts. Over five years the estimated NPV DHB impact would be approximately s9(2)(b)(ii), s9(2)(ba)(i) CPB).

Table 2222 Estimated CPB and DHB impact of immunising close contacts of confirmed cases

Item	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Eligible Population	300	300	300	300	300	1,500
Uptake rate (%)	100%	100%	100%	100%	100%	
Patient Population	300	300	300	300	300	1,500
Dosing	2	2	2	2	2	
Unit Price	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	
Total Vaccine Budget Impact	s9(2)(b)	s9(2)(b)	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Administration Unit Cost	$20.51	$20.51	$20.51	$20.51	$20.51	
Total direct cost due to disease saved	-$950	-$1,681	-$2,091	-$2,410	-$2,891	**-$8,337**
Total Administration Budget Impact	**$12,306**	**$12,306**	**$12,306**	**$12,306**	**$12,306**	**$53,065**
Total other health care cost	**$11,356**	**$10,625**	**$10,215**	**$9,896**	**$9,415**	**$45,000**
Total Vaccine Program Costs	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)	s9(2)(b)(ii),

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969)

Notes: Individual year amounts undiscounted. Note there is assumed to be a prevalent pool of patients who would immediately take the vaccine.

6.2 Health Care Resource Utilisation Budget Impact

Vaccination is expected to reduce the number of patients experiencing acute and long-term consequences of IMD and thus associated health care resource utilisation.

Analysis by PHARMAC staff indicated that although this an important outcome of any vaccination program, that relative to vaccination program costs, offsets are anticipated to be relatively small in comparison.

In February 2019, PTAC comment was sought on health care resource utilisation associated with IMD incidence and key sequelae, including physical, neurological, psychological and behavioural (amputation, blindness, hearing (including deafness), anxiety, facial scarring, severe neurological impairment etc.). PTAC noted Olbricht et al (2018), which essentially reported the data used by the supplier for the Bexsero application. PTAC noted it provided high quality evidence regarding the high prevalence of health consequences in terms of mortality, morbidity (Objective ID A1223390).

Given the complexity and time required to precisely define the health care resource utilisation impact of various sub-programs and the largely immaterial impact on final cost-effectiveness results, a simplifying assumption has been used to determine changes in health care resource utilisation associated with recently defined sub-groups.

With relatively similar assumed efficacy for Bexsero irrespective of age, health resource utilisation costs (offsets) are assumed to be proportionate based on the number of patients vaccinated.

6.2.1 Infant '2+1' Program

Table *2323* summarises estimated health care resource utilisation cost offsets. Over five years the estimated NPV DHB impact would be approximately $1.5m.

Table 2323 Estimated Health Care Resource Utilisation Impact of immunising infants

Item	Year 1	Year 2	Year 3	Year 4	Year 5	5-year NPV
Acute Care cost	$139,678	$235,697	$277,117	$301,885	$320,320	$1,070,590
Direct medical long-term sequelae	$18,061	$34,805	$47,162	$58,544	$81,126	$196,826
Long-term caregiving	$9,490	$25,626	$44,596	$65,246	$110,000	$204,099
Public health management and outbreak	$3,789	$6,385	$7,493	$8,148	$9,019	$29,222
Total direct cost	**$171,018**	**$302,513**	**$376,368**	**$433,823**	**$520,465**	**$1,500,738**

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969)

Notes: Individual year amounts undiscounted. Note there is assumed to be a prevalent pool of patients who would immediately take the vaccine.

6.2.2 Entrants to close living situations (13 to 25 years)

Table *2424* summarises estimated health care resource utilisation cost offsets. Over five years the estimated NPV DHB impact would be approximately $226,000.

Table 2424 Estimated Health Care Resource Utilisation Impact of immunising entrants to close living situations (13 to 25 years)

Item	Year 1	Year 2	Year 3	Year 4	Year 5	5-year NPV
Acute Care	$21,009	$35,451	$41,680	$45,406	$48,179	$161,025

Direct medical long-term sequelae	$2,717	$5,235	$7,094	$8,805	$12,202	$29,604
Long-term caregiving saved	$1,427	$3,854	$6,708	$9,813	$16,545	$30,698
Public health management and outbreak	$570	$960	$1,127	$1,226	$1,357	$4,395
Total direct cost	**$25,722**	**$45,500**	**$56,609**	**$65,250**	**$78,282**	**$225,722**

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969)

Notes: Individual year amounts undiscounted. Note there is assumed to be a prevalent pool of patients who would immediately take the vaccine.

6.2.3 Entrants catch up for ages 13-25 years in close living situations for 1 year only and ongoing entrants

Table *2525* summarises estimated health care resource utilisation cost offsets. Over five years the estimated NPV DHB impact would be approximately $234,000.

Table 2525 Estimated Health Care Resource Utilisation Impact of immunising catch up for ages 13-25 years in close living situations for 1 year only and ongoing entrants

Item	Year 1	Year 2	Year 3	Year 4	Year 5	5-year NPV
Acute Care	$68,267	$26,589	$31,261	$34,055	$36,135	$173,282
Direct medical long-term sequelae	$8,827	$3,926	$5,320	$6,604	$9,152	$28,994
Long-term caregiving saved	$4,638	$2,891	$5,031	$7,360	$12,409	$26,592
Public health management and outbreak	$1,852	$720	$845	$919	$1,017	$4,721
Total direct cost	**$83,584**	**$34,126**	**$42,458**	**$48,939**	**$58,713**	**$233,589**

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969)

Notes: Individual year amounts undiscounted. Note there is assumed to be a prevalent pool of patients who would immediately take the vaccine.

6.2.4 Special high-risk immunocompromised groups - same as ACWY high-risk criteria)

Table *2626* summarises estimated health care resource utilisation cost offsets. Over five years the estimated NPV DHB impact would be approximately $24,000.

Table 2626 Estimated Health Care Resource Utilisation Impact of immunising One year catch-up for ages 5-21 years

Item	Year 1	Year 2	Year 3	Year 4	Year 5	5-year NPV
Acute Care	$4,915	$4,801	$5,645	$6,150	$6,525	$23,878
Direct medical long-term sequelae	$635	$709	$961	$1,193	$1,653	$4,277

Long-term caregiving	$334	$522	$908	$1,329	$2,241	$4,298
Public health management and outbreak	$133	$130	$153	$166	$184	$651
Total direct cost	**$6,017**	**$6,162**	**$7,667**	**$8,837**	**$10,602**	**$33,104**

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969)

Notes: Individual year amounts undiscounted. Note there is assumed to be a prevalent pool of patients who would immediately take the vaccine.

6.2.5 Close contacts of confirmed cases

Table *2727* summarises estimated health care resource utilisation cost offsets. Over five years the estimated NPV DHB impact would be approximately $8,000.

Table 2727 Estimated Health Care Resource Utilisation Impact of Close contacts of confirmed cases

Item	Year 1	Year 2	Year 3	Year 4	Year 5	5-year NPV
Acute Care	$776	$1,309	$1,540	$1,677	$1,780	$5,948
Direct medical long-term sequelae	$100	$193	$262	$325	$451	$1,093
Long-term caregiving	$53	$142	$248	$362	$611	$1,134
Public health management and outbreak	$21	$35	$42	$45	$50	$162
Total direct cost	**$950**	**$1,681**	**$2,091**	**$2,410**	**$2,891**	**$8,337**

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969)

Notes: Individual year amounts undiscounted. Note there is assumed to be a prevalent pool of patients who would immediately take the vaccine.

6.3 Total Budget Impacts

Table 2828 summarises net budget impacts of all vaccination programs.

Table 2828 Summary: Estimated Net Budget Impact of Vaccination Programs - aggregate of vaccine program implementation and change in health care resource utilisation costs

Program	Year 1	Year 2	Year 3	Year 4	Year 5	5-year NPV
Infant '2+1' program.	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Entrants to close living situations (13 to 25 years).	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Entrants catch up for ages 13-25 years in close living situations for 1 year only and ongoing entrants as above.	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),

Special high-risk immunocompromised groups - same as ACWY high risk criteria.	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)
Close contacts of confirmed cases.	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)	s9(2)(b)(ii),	s9(2)(b)	s9(2)(b)(ii),

Source: "Meningococcal B_MARCH_2020_CUA_BIA" (Objective ID A1345969)

Notes: Individual year amounts undiscounted. Note there is assumed to be a prevalent pool of patients who would immediately take the vaccine.

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Attachment One: CUA Review: Bexsero - Prevention of meningococcal disease - Infant Schedule (2+1 dosing)

Model Input/ Assumption	Questions	PHARMAC Comment
Type of analysis	What type of analysis was undertaken (i.e., cost-utility analysis (CUA) or cost-minimisation analysis (CMA))? Was this appropriate?	A CUA was undertaken. This was appropriate given the proposed treatment and comparator (see below) and clinical claim.
Target population	Was the analysis based on the correct target population (i.e. the target population most likely to receive treatment, reflecting the clinical treatment algorithm and place in therapy in New Zealand)?	Applicant submitted for an infant population (i.e. aged 12 months). In terms of those proposed for prophylactic vaccination, this was correctly identified. Submission model however also identifies the infectious nature of the disease and also appropriately considers the broader 'target population', i.e., those in the infant group not directly vaccinated, along with the broader New Zealand population. This is subsequently reflected in the model structure and approach ('Health States and Model Structure' below).
Treatment regimen (including dose)	Does the analysis describe all relevant treatment paths? Is the correct pharmaceutical dosage used? Are there likely to be dose adjustments (including frequency) over time? Does the analysis need to consider previous or subsequent lines of therapy?	The vaccination is a prophylactic treatment. This is correctly identified. The submission correctly notes there are no currently funded vaccines and correctly identifies 'treatment' of meningococcal B patients. The submission provides for both a '3+1' and a '2+1' treatment schedule. Both are appropriate options and are separately analysed. Analysis does not need to consider previous or subsequent lines of therapy.
Comparator	Have the appropriate comparator(s) been used in the analysis? Is this the treatment that most prescribers would replace in NZ clinical practice, and the treatment prescribed to the largest number of patients (if this differs from the treatment most prescribers would replace)? What is the current treatment paradigm? Does the analysis need to consider previous or subsequent lines of therapy?	The vaccination is a prophylactic treatment. This is correctly identified. The comparator of no vaccination is correctly identified (i.e., no currently funded vaccine on the New Zealand National Immunisation Schedule (NIS)). Meningococcal disease can be treated with recommended antibiotics (benzyl penicillin and amoxycillin), but early treatment is vital. Again, this submission acknowledges this. The analysis does not need to consider previous or subsequent lines of therapy. The submission appropriately accounts for this.

Model Input/ Assumption	Questions	PHARMAC Comment
Efficacy	Is the model based on the best-quality data available? Were the sources of data used in the model clearly stated? Is there any evidence to suggest selective use of data? Is the primary evidence used adequately outlined?	The supplier ultimately identified three randomised, multicentre trials that provide the primary evidence for the safety and immunogenicity of 4CMenB for the prevention of IMD. The updated search included level I and II evidence only. The literature search was tailored to identify relevant clinical trials for 4CMenB vaccine in infants according to the requirements for systematic literature reviews of the UK's National Institute for Health and Care Excellence (NICE). The search was designed to identify double-blind, single-blind, and open-label RCTs and systematic reviews using databases including OVID (Medline and EMBASE), Cochrane, and clinicaltrials.gov. Being an update of a previous search, the literature search was limited from 2013 until 27th July 2017 (the date of the search). It also presented an English national observation cohort study of vaccine effectiveness, a study assessing the coverage of meningococcal strains by 4CMenB for isolates obtained during 2007-08 and 2014-15 in England and Wales, using the Meningococcal Antigen Typing System (MATS) and vaccine efficacy waning. PTAC considered the presented evidence in February 2019. The Committee considered that there is no direct evidence from randomised controlled trials that 4CMenB vaccination reduces rates of invasive meningococcal disease. The Committee considered there is indirect evidence of 4CMenB effectiveness and that evidence for health benefits that may be gained from 4CMenB were of good strength and quality. It is considered that best available evidence has been identified and presented in the submission. It is considered the submission reflects a comprehensive search for data relevant to modelling the treatment's economic value.
Time horizon and cycle length	Were the time horizon and cycle length appropriate and justified in terms of the	Time horizon of 100 years identified, with yearly cycles.

Model Input/ Assumption	Questions	PHARMAC Comment
	underlying disease and the effect of interventions?	PHARMAC staff deem this appropriate in terms of estimated duration of protection (in years), the nature and operation of the prepared model (transmission dynamic model with members of cohort annually vaccinated) and the intended population perspective of the analysis.
Health states and model structure	Has the model type (e.g. decision analytic model or Markov model) been described and justified? Is justification of the choice of health states within the model provided? Have any important health states been omitted from the model? If so, is this justified? Is the model transparent? Does the model appear to be unnecessarily complicated or simplified too much?	The submission presents a population-based transmission dynamic model. A transmission dynamic model aims to instantaneously capture and trace the movement of the disease across the population as a function of numerous, dynamic, interacting epidemiological factors. This is described in two parts in detail, with an 'input-output' conceptual framework. Firstly, it specifies the key drivers of how as an infectious disease, meningococcal is spread in the population, including IMD epidemiology, vaccination strategy, population contact patterns and bacterium carriage rates. Secondly, as a function of 'vaccination strategy' and 'no vaccination strategy', these are converted into model 'outputs', that is acute cases, hospitalisations, case fatalities and long-term sequelae cases. The use of the model approach is conceptually justified with reference to previous use for other meningococcal disease serogroups and the acceptance of the modelling approach by evaluators in the UK and Australia. PHARMAC staff note the guidance of section 5.4 of the PFPA (v.2.2). While this section does not explicitly recommend or endorse use of transmission dynamic models, it does state static models may be appropriate if herd immunity does not play a significant role in the assessment. As such, PHARMAC staff, given the submission claim and assumption of prevention of case transmission in the economic model, can appreciate the rationale for the approach taken by the supplier. The model document presents the model structure as a tree diagram. For each incident case of vaccine-preventable IMD and for each vaccination strategy, clinical and economic outcomes are captured using a decision tree model with branches for various outcomes, including long-term sequelae and

Model Input/ Assumption	Questions	PHARMAC Comment
		mortality. The probability of these sequelae is assumed to be independent of each other, creating a transparent, but complex model structure. The resulting proportion of patients for each specified age group ultimately residing in these combinations of acute case/sequelae/mortality are also presented, effectively as numerous 'health states'. Health states are appropriately justified with reference to the health outcomes; however, their presentation is arguably unnecessarily complex, particularly with reference to the long-term sequelae health states presented. The model overall is exceptionally complex. The model is presented in Excel and consists of 136 spreadsheets. Whilst attempting to precisely capture the dynamics of infectious disease transmission and subsequent outcome differences between the treatment and comparator arms, the model is wieldy, and time consuming to understand and navigate. The model is accompanied by a user guide which in itself is lengthy and detailed. The model is operated by macro buttons, with subsequent model analysis generated by VBA coding. Inputs, intermediate outputs and final results are displayed across the spreadsheets. However, intermediate outputs and final results are often presented without formulas or cell references, making tracing the transition of original model inputs to outputs either impossible or time-consuming. The size and operation of the model ultimately inhibit its transparency and understandability, making it difficult and/or time consuming to ultimately validate the economic evaluation outcome claims.
Key parameters and assumptions	Was the correct discount rate (3.5%) used? Was the discount rate appropriately applied to both the costs and utility values? Was the discount rate appropriately applied to both arms of the model?	A 3.5% discount rate is applied to both costs and benefits in both arms of the model on an annual basis in accordance with the annual model cycles. However, as above in "Health States and Model Structure", tracing the transition of original model inputs to outputs is either impossible or time-consuming, making it difficult to determine if discounting is appropriately applied in the model.

Model Input/ Assumption	Questions	PHARMAC Comment
	Was the discount rate adjusted appropriately for the model cycle length? Has age of model entry been specified? Has a half-cycle correction been included? If not, what justification is given?	The age of model entry is not explicitly specified. It is not clear if half-cycle correction has been incorporated into the model, nor is it explicitly referenced.
Transformation and extrapolations	Is the adaption of efficacy data into model inputs clear and adequately detailed? Does the analysis extrapolate data to the longer term, or extrapolate intermediate clinical endpoints to final outcomes? If so, is this appropriate, justified, and modelled using the correct methodology? Was this tested in the sensitivity analysis? Have data from different sources been combined? If so, are the data compatible and combined using appropriate methodology? Is there a clear and reasonable justification of how data have been incorporated into the model (i.e. the methodology used in the calculation of probability values)? Have the probability values been calculated accurately given cycle length?	Assumed vaccine efficacy, coverage (uptake), MATS assay rate (i.e., the ability of the vaccine to match given serogroup strain), vaccine waning by age (i.e., effective duration of protection) and efficacy against carriage (and thus herd immunity effect) are clear and detailed. These inputs have come from clearly identified sources. However, it is unclear on first sight how these key drivers of treatment effect operate (i.e., how they generate an ultimate vaccine coverage protection rate assumed for analysis). As above in “Health States and Model Structure”, tracing the transition of original model inputs to outputs is either impossible or time-consuming. This includes determining whether probability values have been calculated in accordance with cycle length.
Health-Related Quality of life	How was quality of life measured? Was this method justified? If subjective values were used, were these validated and tested in the sensitivity analysis?	A systematic literature review was undertaken to determine appropriate utility values for acute case events and sequelae cases (reflecting specific sequelae outcomes). The applicant notes no literature identified quality of life values specific to serogroup B; nonetheless it notes consultation with New Zealand experts deems this approach to be reasonably appropriate. The proposal considered both sequelae and non-sequelae specific utility values in

Model Input/ Assumption	Questions	PHARMAC Comment
	Have New Zealand specific values been able to be sourced? If not from where and is/how is this justified? Were the estimated utility values reasonable? Have they been compared to those from other sources or diseases with similar qualitative impacts on quality of life?	deriving rates for the model, from a variety of countries. Among the identified studies with relevant sequela-specific utilities weights, the highest priority was given to studies using the EQ-5D (EuroQol–five-dimension scale) instrument. Selection of studies was then narrowed by whether the utility weight was derived using a generic descriptive instrument (ie, EQ-5D, Health Utilities Index (HUI), SF-6D or SF-36/R and 36 if converted into SF-6D) or directly from a patient preference elicitation. For certain sequelae, ultimate selection of utility weights derived using the EQ-5D instrument were prioritised. Sequelae weights were subsequently used to create an aggregate long-term sequelae utility value. PHARMAC staff reviewed this approach and the ultimate values generated and deemed them reasonably appropriate, albeit in some instances understating the quality of life impact of long-term sequelae. PHARMAC staff note the 'revised scenario' (i.e., non-PFPA guideline) model also assumes quality of life is impacted as follows: • Use of a quality-adjustment factor (as done in UK analyses presented to the Joint Committee of Vaccination and Immunisation) • Utility loses for parents and families of patients with sequelae or who die. PHARMAC, in accordance with its methodological approach to pharmacoeconomic analysis outlined in the PFPA, does not practise using QAFs to reflect the severity or seriousness of given conditions or the patient populations in which they occur. They would not be considered appropriate for PHARMAC decision making. PHARMAC also consider that counting both a reduction in caregiver utility and a direct cost for caregiving of those patients with long-term sequelae as methodologically inappropriate; only utility or cost impacts should be captured.
Pharmaceutical cost	Were pharmaceutical costs calculated correctly?	Vaccine costs were entered correctly. However, as above in "Health States and Model Structure", tracing the transition of

Model Input/ Assumption	Questions	PHARMAC Comment
	Were there any rebates that have not been included?	original model inputs to outputs is either impossible or time-consuming, making it difficult to determine if ultimate cost outcomes for vaccine is correctly applied or calculated. Rebates were not included (this was not deemed relevant).
	Is a generic pharmaceutical likely to become available in the near future? (see PFPA for more information)	Generic vaccines are not relevant to assessment at this stage.
	What dose was used in the cost calculations and where was this information sourced? (Note that the dose should be based on the dose used in the key clinical trials unless there is evidence of efficacy for different doses in clinical practice.)	Vaccine doses were correctly applied in accordance with age based dosing requirements for Bexsero. The analysis considered both a '3+1' and a '2+1' strategy. No dosing adjustments are provided for. Body weight is not relevant to calculation of treatment costs.
	Are there likely to be dose adjustments over time (including frequency)?	Wastage is not explicitly provided for. The model assumes a specified rate of population uptake. However, analysis does not appear to consider sensitivity scenarios around ultimate patient uptake in the defined patient population.
	If relevant, was the correct bodyweight used in the calculation of pharmaceutical cost?	
	Is there likely to be any pharmaceutical wastage? (This may occur due to inappropriate vial size, non-compliance, or if infusions cannot be stored once prepared).	
Pharmacy costs	Were pharmacy handling and service fees included for pharmaceuticals dispensed at a community pharmacy?	None of the pharmacy costs outlined here were considered by the analysis.
	Were pharmacy margin and pack fees included?	
	Was the patient prescription co-payment included? ($5 people aged 13 years and over).	

Model Input/ Assumption	Questions	PHARMAC Comment
	Are there any pharmaceutical part-charges associated with co-administered or comparator treatments?	
Other relevant costs	How is the pharmaceutical administered? Have all costs associated with administration been taken into account? Have primary health care costs been calculated correctly? (This should include both the patient co-payment and government contribution). Have hospital costs been calculated correctly using NZ DRG cost weights? Were these volume-adjusted? Are you aware of any costs that appear to be inaccurate? Have any important and relevant costs been excluded? Has this been justified? Do disease management costs differ between treatment and comparator? Has this been justified?	The vaccine is assumed to be administered by a nurse. PHARMAC staff view this assumption as appropriate. The submission assumes the 'booster' dose of the treatment regimen to incur an administration cost, while the initial doses are scheduled with existing NIS timeframes and thus do not incur an additional cost. The proposal assumes a nursing cost reflecting the immunisation subsidy of $22.93 per administration as stated on PHARMAC Cost Resource Manual. PHARMAC staff note this has fallen slightly to $20.51 since the application was made. PHARMAC staff note the acute care and long-term sequelae cost items outlined in analysis as broadly appropriate. There do not appear to be any material costs that have been excluded. Disease management costs do not appear to differ between treatment and comparator; however, it is unclear how these were applied in the model. As above, intermediate outputs and final results are often presented without formulas or cell references, making tracing the transition of original model inputs to outputs either impossible or time-consuming. PHARMAC staff note long-term care giving and economic productivity costs of illness have been included in analysis. As per the PFPA, only direct healthcare costs should be included in economic analysis, as such productivity costs should be excluded from consideration. PHARMAC also consider that counting both a reduction in caregiver utility and a direct cost for caregiving of those patients with long-term sequelae as methodologically inappropriate; only utility or cost impacts should be captured.

Model Input/ Assumption	Questions	PHARMAC Comment
Results	Was the estimated QALY per $1 million invested reported as a range as well as a point estimate? Were likely and possible range estimates provided? Were there any important factors that have been excluded from the analysis that could have an impact on the results? In your opinion, are the conclusions of the analysis justified? Is it reproducible, i.e., can the model results be reproduced from scratch?	QALYs per $m point estimates were reported for the '3+1' and '2+1' vaccine regimen scenarios, both as per the guidance of the PFPA and separate from the PFPA (i.e., incorporating factors not prescribed for, e.g. the use of a societal perspective, incorporation of productivity losses, use of QAF, etc.). No likely and possible range estimates were provided (although sensitivity analyses were undertaken, see below). Overall, PHARMAC consider no important factors have been excluded from analysis that could impact results materially from those presented. Rather, generally speaking, PHARMAC staff feel assumptions or inputs should be removed or modified. Ultimately base case point estimates presented likely reasonably approximate cost-effectiveness, albeit perhaps overstating results for several reasons, including lack of direct vaccine efficacy data, assumptions made regarding duration of vaccine protection and the incorporation of herd immunity benefits. PHARMAC staff consider there to be challenges in reproducing the model results from scratch, including the complexity of the presented model. Replicating the same transmission dynamic model would be a significant undertaking; PHARMAC staff view a simpler modelling approach may yield similar cost-effectiveness results.
Sensitivity analysis	Were all key inputs and assumptions varied in the sensitivity analysis (including those uncertain or with a material impact on outcomes)? Were the range and choice of variables used in the sensitivity analysis justified? Were the results of the sensitivity analysis interpreted correctly?	All relevant key inputs and assumptions were varied in the sensitivity analysis. However, sensitivity analysis is only presented for the '3+1' PFPA Guideline vaccine regimen scenario (i.e., not for the '2+1' scenario). It should be noted treatment costs (vaccine and administration) are a material portion of costs considered in analysis. Choices of variable were justified and appropriate. PHARMAC notes the QALY per million results of the '3+1' sensitivity analysis presented in diagrams as reasonably appropriate, indicating the values used are realistic, as well as providing a realistic reflection of the cost-effectiveness of treatment.

Model Input/ Assumption	Questions	PHARMAC Comment
	Given the sensitivity analysis, are the chosen likely and possible CUA ranges reasonable?	Varying values and assumptions used in sensitivity analysis is hampered by the limited operability of the model. As such, this makes it hard to manually validate the outcomes. However, PHARMAC staff would also note some of the cost-effectiveness outcomes referenced in the text do not align with those in the diagrams (for example the impact of varying discounting between 0 and 5%). Overall, PHARMAC staff consider the likely and possible ranges presented in diagrams in the submission body as plausible, albeit unverifiable and inconsistently presented.
Analysis	Did the analysis list any factors that could limit the applicability of the results (e.g. differences in patient population)? Were any caveats placed on analysis outcomes (e.g. awaiting further evidence appraisal or other events (e.g. pricing offers)? How could the analysis be improved? Describe the overall quality of the report.	The applicant notes, "*There is often limited availability of data for relevant parameters and assumptions need to be made about the likely value of these parameters and the variability that may exist around them as in the present evaluation. The health economic analysis currently relies on data showing the real-world effectiveness of 4CMenB where it was implemented in a national immunisation programme in infants in the UK.*" The applicant notes in presenting results for both the PFPA-Guidelines based analysis and a broader, more societal perspective, consideration should be given to the impact of disease beyond the immediate patient. Overall, the cost-effectiveness analysis, including its report, is of mixed quality. The submission is sufficiently detailed in outlining process and assumptions underpinning the model and its operation. The model structure, including how it captures the transmission of the disease, is deemed conceptually appropriate. However, the robustness of the ultimate analysis, including the impact of varying assumptions and inputs, is unclear, given the

Model Input/ Assumption	Questions	PHARMAC Comment
		extreme complexity, lack of transparency and ultimate operability of the presented model. PHARMAC staff consider the base case estimates are a likely reasonable approximation of ultimate cost-effectiveness, but that sensitivity analysis outcomes are difficult to verify with confidence.

PHARMAC
TE PĀTAKA WHAIORANGA

MEMORANDUM FOR BOARD MEETING 2 DECEMBER 2022

To:	Pharmac Directors
From:	Chief Executive
Date:	November 2022
Item:	8.4

GSK multiproduct proposal to widen access to meningococcal B vaccine and secure ongoing supply of zoster vaccine

Recommendations

It is recommended that, having regard to the decision-making framework set out in Pharmac's Operating Policies and Procedures, you:

resolve to amend the restriction for meningococcal B multicomponent vaccine (Bexsero) inj 175 mcg per 0.5 ml prefilled syringe in Section I of the Pharmaceutical Schedule from 1 March 2023 as follows (additions in bold, deletions in strikethrough):

Any of the following:

1. Three doses for children up to 12 months of age (inclusive) for primary immunisation; or

2. Up to three doses (dependent on age at first dose) for a catch-up programme for children from 13 months to 59 months of age (inclusive) for primary immunisation, from 1 March 2023 to 31 August 2025; or

~~Either:~~

~~1. Both:~~

~~1. Child is under one year of age; and~~

~~2. Any of the following:~~

~~a) up to three doses for patients pre- and post-splenectomy and for patients with functional or anatomic asplenia, HIV, complement deficiency (acquired or inherited), or pre- or post-solid organ transplant; or~~

~~b) up to three doses for close contacts of meningococcal cases of any group; or~~

~~c) up to three doses for child who has previously had meningococcal disease of any group; or~~

~~d) up to three doses for bone marrow transplant patients; or~~

~~e) up to three doses for child pre- and post immunosuppression*; or~~

3. Both:
   1. Person is one year of age or over; and
   2. Any of the following:
      a) up to two doses and a booster every five years for patients pre- and post-splenectomy and for patients with functional or anatomic asplenia, HIV, complement deficiency (acquired or inherited), or pre- or post-solid organ transplant; or
      b) up to two doses for close contacts of meningococcal cases of any group; or
      c) up to two doses for person who has previously had meningococcal disease of any group; or
      d) up to two doses for bone marrow transplant patients; or
      e) up to two doses for person pre- and post-immunosuppression***; or**

4. Both:

a) Person is aged between 13 and 25 years (inclusive); and

b) Either:

i. Two doses for individuals who are entering within the next three months, or in their first year of living in boarding school hostels, tertiary education halls of residence, military barracks, or prisons; or

ii. **Two doses for individuals who are currently living in boarding school hostels, tertiary education halls of residence, military barracks, or prisons, from 1 March 2023 to 28 February 2024.**

*Immunosuppression due to corticosteroid or other immunosuppressive therapy must be for a period of greater than 28 days.

resolve to amend the Indication Restriction for meningococcal B multicomponent vaccine (Bexsero) inj 175 mcg per 0.5 ml prefilled syringe in Part II of Section H of the Pharmaceutical Schedule from 1 March 2023 as follows (additions in bold, deletions in strikethrough):

Restricted
Initiation – Primary immunisation for children up to 12 months of age
Therapy limited to three doses
Either*:*

1. **Three doses for children up to 12 months of age (inclusive) for primary immunisation; or**
2. **Up to three doses (dependent on age at first dose) for a catch-up programme for children from 13 months to 59 months of age (inclusive) for primary immunisation, from 1 March 2023 to 31 August 2025**

~~Initiation – Infants under one year of age~~
~~Any of the following:~~

~~1. up to three doses for patients pre- and post-splenectomy and for patients with functional or anatomic asplenia, HIV, complement deficiency (acquired or inherited), or pre- or post-solid organ transplant; or~~
~~2. up to three doses for close contacts of meningococcal cases of any group; or~~
~~3. up to three doses for child who or has previously had meningococcal disease of any group; or~~
~~4. up to three doses for bone marrow transplant patients; or~~
~~5. up to three doses for person pre- and post-immunosuppression*~~

Initiation – Person is one year of age or over
Any of the following:

1. up to two doses and a booster every five years for patients pre- and post-splenectomy and for patients with functional or anatomic asplenia, HIV, complement deficiency (acquired or inherited), or pre- or post-solid organ transplant; or
2. up to two doses for close contacts of meningococcal cases of any group; or
3. up to two doses for person who has previously had meningococcal disease of any group; or
4. up to two doses for bone marrow transplant patients; or
5. up to two doses for person pre- and post-immunosuppression*

Initiation – Person is aged between 13 and 25 years (inclusive)
Therapy limited to two doses
Both

1. **Person is aged between 13 and 25 years (inclusive); and**
2. **Either:**
   - 2.1. **Two doses for individuals who are entering within the next three months, or in their first year of living in boarding school hostels, tertiary education halls of residence, military barracks, or prisons; or**
   - 2.2. **Two doses for individuals who are currently living in boarding school hostels, tertiary education halls of residence, military barracks, or prisons, from 1 March 2023 to 28 February 2024.**

*Immunosuppression due to corticosteroid or other immunosuppressive therapy must be for a period of greater than 28 days.

resolve to approve the 21 October 2022 agreement with GlaxoSmithKline NZ Limited.

resolve that the consultation on this proposal was appropriate, and no further consultation is required.

Purpose

This paper seeks a decision from the Board on a significant pharmaceutical investment transaction that would widen access to an existing listing and secure ongoing supply for another existing listing.

Strategic Direction

The proposal is to change the listings of existing medicines in the Pharmaceutical Schedule, which aligns with our purpose to deliver the best health outcomes from New Zealand's investment in medicines and medical devices by making choices and managing expenditure and supply.

This proposal would provide better health outcomes for all New Zealand tamariki by providing them protection against potentially life-threatening invasive meningococcal B disease. The proposal would also secure ongoing supply of zoster vaccine, ensuring that people who are 65 years of age would continue to be protected against herpes zoster (shingles).

Why proposal should not be considered under Delegated Authority

The proposal outlined in this Board paper has not been dealt with by the Chief Executive under delegated authority because the estimated Financial Impact (NPV) of this proposal is more than $10,000,000 of the Pharmaceutical Budget. The Financial Impact (NPV) is calculated on the basis of the net present value of the proposed subsidy (ex-manufacturer exclusive of GST) over five years at a discount rate of 8% to be paid by the funder for the product(s) and the forecast demand, taking into account any effect of the change /decision on that demand, versus the status quo.

Executive Summary

- This multiproduct proposal is to widen access for meningococcal B vaccine (Bexsero) and secure ongoing supply of zoster vaccine (Shingrix).
- Direct negotiations with GSK were successful in reaching a commercial arrangement that would generate savings on zoster vaccine to the Combined Pharmaceutical Budget in this financial year and over the next five years, and help meet the health needs of people who are at risk from invasive meningococcal disease or shingles. The proposal is also expected to result in increased immunisation claim costs for the Ministry of Health as there would be more immunisation clinic visits to access meningococcal B vaccine.
- This multiproduct proposal is ranked s9(2)(b) on the current Options for Investment list (September 2022). The overall CPB impact of this proposal would be s9(2)(b)(ii), s9(2) over 5 years (NPV, 8% discount rate). Higher costs are anticipated in the first two full years of the proposal, resulting from the large catch-up cohorts. Costs of $10.2 million would be incurred by Te Whatu Ora as part of this proposal, to fund the increased immunisation claim costs from increased vaccination events. Te Whatu Ora aware of the increased costs it would incur and advised in its consultation response that it is supportive of the proposal.

- Pharmac staff consider that widened access for meningococcal B vaccine would be equity enhancing. We know that Māori and Pacific people have higher rates of meningococcal infection than non-Māori non-Pacific people. Access to meningococcal B vaccine is currently mainly through the private market (excepting for a small group of immunocompromised patients who have funded access), which creates a cost barrier for those unable to afford it. Te Whatu Ora would be responsible for the implementation of this proposed funding decision through National Immunisation Programme. While funding decisions ensure that vaccine is available for use in the programme, a successful immunisation programme could strongly influence equity of access by ensuring services are targeted to priority groups within the overall funded population. Pharmac staff work closely with the National Immunisation Programme to support their implementation activities.

- Detailed consultation feedback was received from advocacy groups, clinicians, Te Whatu Ora, the Public Health agency, Te Whatu Ora hospitals, the National Vaccines Taskforce, suppliers and consumers. Responders were generally supportive and requested further widened access for both meningococcal B and zoster vaccines. We will take these suggestions on board for future considerations of wider access to these vaccines.

The Proposal

This proposal is to widen access to meningococcal B vaccine (Bexsero) in the Pharmaceutical Schedule from 1 March 2023 to protect against meningococcal disease in the following groups:

- children up to 12 months of age administered as part of the childhood immunisation programme

- people aged 13 to 25 years who are entering into or in their first year of specified close-living situations

- catch-up programmes for both these groups.

The proposal would also secure ongoing supply and a reduced price of zoster vaccine (Shingrix) from 1 December 2022. No changes are proposed to the current eligibility criteria for zoster vaccine.

The proposal includes amendments to the contractual arrangements for these two vaccines as follows:

- net price reduction for meningococcal B vaccine, which is currently funded subject to eligibility criteria for individuals at high-risk from invasive meningococcal B disease, and protection from subsidy reduction and delisting until 28 February 2026

- net price reduction for zoster vaccine, which is currently funded subject to eligibility criteria for individuals who are 65 years of age, and protection from subsidy reduction and delisting until 28 February 2026.

s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j) [redacted]
s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j) [redacted]
s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j) [redacted]
s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j) [redacted]
s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j) [redacted]

The provisional agreement, conditional on consultation and approval, between GSK and Pharmac dated 21 October 2022 can be made available to any Board member upon request.

Budget Impact Summary

The financial implications of this proposal are outlined in the Cost and Savings discussion under the Factors for Consideration section of this paper. The Summary budget impact analyses for each individual medicine included in the proposal can be found in Appendix One and the overall multiproduct proposal budget impact analysis is outlined in the table below. Overall, the multiproduct proposal would be a net cost to the Combined Pharmaceutical Budget (CPB).

SUMMARY OF PROPOSAL						
Market data	**Year ending**	**30 Jun 2023**	**30 Jun 2024**	**30 Jun 2025**	**30 June 2026**	**30 June 2027**
Estimated number of patients affected by proposal		56,650	145,691	134,557	59,480	59,601
Estimated number of Māori or PI people affected by proposal		24,299	50,497	48,029	29,242	29,713
Community Pharmaceutical Expenditure	Expenditure (gross)	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
	Expenditure (net)	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
	Net present value (NPV)	s9(2)(b)(ii),				
TOTAL - Combined Pharmaceutical Budget	Net cost to CPB	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
	Net present value (NPV)	s9(2)(b)(ii),				
Other (Non-Pharmaceutical) Health Sector Costs	Net distribution costs	$0	$0	$0	$0	$0
	Other (non-pharmaceutical) Health Sector costs	($700,000)	$4,670,000	$4,360,000	$170,000	$170,000
	Net other Health Sector costs	($700,000)	$4,670,000	$4,360,000	$170,000	$170,000
	Net present value (NPV)	$7,600,000				
Total - Pharmaceutical and Health Sector Costs	Total cost (savings) to Health Sector including CPB cost	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
	Net present value (NPV)	s9(2)(b)(ii),				

Notes:
* Number of patients anticipated to be immunised with meningococcal B or zoster vaccines
# Includes patients receiving treatment and patients new to treatment
1. Expenditure (gross) = forecast of spending at the proposed price and subsidy.
2. Net cost to CPB = forecast of change in spending compared with status quo.
3. Hospital pharmaceutical expenditure is not included as this is anticipated to be negligible
4. All pharmaceutical costs are ex-manufacturer.
5. All costs are ex-GST.
6. NPV is calculated over five years using an annual discount rate of 8%.
7. Calculations are in A1630409 and Appendix One.
8. Total costs to Health Sector include Pharmac and Te Whatu Ora costs.

The table below shows the costs or savings of each medicine to the CPB (excluding sector costs or offsets). All pharmaceutical expenditure is in the community:

Costs and savings to the CPB of individual components of the multiproduct proposal

Product	**Current net costs 5-Year NPV**	**Proposal net costs 5-Year NPV**	**Proposal net Savings 5-Year NPV**
Meningococcal B vaccine	s9(2)(b)(ii),	s9(2)(b)(ii),	s9(2)(b)(ii),
Shingles vaccine	s9(2)(b)(ii),	s9(2)(b)(ii), s9(2)	s9(2)(b)(ii),
Total investments/savings		s9(2)(b)(ii),	s9(2)(b)(ii), s9(2)
Total Net Financial Impact (NPV, 5 years)		s9(2)(b)(ii),	

Proposal commercial considerations

This bundle proposal

- In June 2022 GSK approached Pharmac with a multiproduct proposal that included widened access to meningococcal B vaccine and a reduction in price for the zoster vaccine. The proposal offered tiered pricing for several options for different levels of widened access to meningococcal B vaccine.

Meningococcal B vaccine

- Meningococcal B vaccine (Bexsero) provides active immunisation against invasive disease caused by *N. meningitidis* group B strains. It has been funded since July 2021 for people who are at high risk from meningococcal group B infection and close contacts of meningococcal cases.

- A funding application for meningococcal B vaccine was received in February 2018. We received advice from the Pharmacology and Therapeutics Advisory Committee (PTAC) and the Immunisation Subcommittee (now the Immunisation Advisory Committee) that meningococcal B vaccine should be funded for a range of groups, including: close contacts of cases, high-risk immunocompromised people, entrants to close living situations [13 to 25 years] (with or without catch-up) and inclusion in the infant immunisation schedule.

- [redacted]

- An RFP for Various Vaccines was issued on 11 November 2022. This RFP is usually issued every three to four years to secure supply of most of the vaccines listed in the Pharmaceutical Schedule. The 2022 RFP would secure supply of vaccines from 1 July 2024 until 30 June 2027. Meningococcal B vaccine was not included in the RFP as we are proposing to widen access through this proposed multiproduct bundle agreement with GSK which includes protection from subsidy reduction and delisting until 28 February 2026.

- This proposal secures early savings on zoster vaccine and a reduced price for meningococcal B vaccine, making both more cost effective. This multiproduct proposal also allows the broader funding of the meningococcal B vaccine, as the bundle was ranked [redacted] while the individual meningococcal B vaccine proposals were ranked [redacted]

Zoster vaccine

- Zoster vaccine (Shingrix) is an adjuvanted recombinant vaccine that provides protection against herpes zoster (shingles) and post-herpetic neuralgia.

- In August 2020 Merck Sharpe and Dohme (MSD) advised Pharmac that it would be discontinuing its funded zoster vaccine (Zostavax) as it was converting its zoster manufacturing sites over to manufacture of its developmental COVID-19 vaccine.

MSD subsequently advised in 2021 that it had stopped development of its COVID-19 vaccine but was still discontinuing its zoster vaccine.

- GSK submitted a funding application for Shingrix in April 2022 and this was considered by the Immunisation Advisory Committee at its May 2022 meeting. The Committee considered that Shingrix would be an appropriate alternative to Zostavax in the event of discontinuation of Zostavax or following a commercial process. It also considered that there would be a significant unmet health need if a zoster vaccine was no longer funded.

- GSK submitted this multiproduct bundle proposal in June 2022, including a substantial discount for Shingrix and widened access for Bexsero.

- Shingrix was subsequently funded from August 2022 for people who are 65 years of age (no change to the eligibility criteria). The list price of s9(2) per dose was substantially higher than that for Zostavax, and the additional cost was attributed to the COVID-19 Response and Recovery Fund since the Zostavax discontinuation was related to COVID-19 issues. Pharmac purchased 12,000 doses of Shingrix at a total cost of s9(2)(b)(ii), to secure 2-3 month's supply while Pharmac staff continued working to finalise a listing agreement for Shingrix at a reduced price.

- Pharmac staff subsequently successfully negotiated a Letter of Agreement with GSK to secure an additional 25,000 doses of Shingrix s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j)
s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j)
s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j)
s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j)
s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j)
s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j)
s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j)

- Zoster vaccine has not been included in the recently released vaccines RFP as we are proposing to instead secure ongoing supply through this proposed multiproduct bundle agreement with GSK, which includes protection from subsidy reduction and delisting until 28 February 2026. This proposal would secure early savings on zoster vaccine and a reduced price for meningococcal B vaccine, making both more cost effective. As noted above, the offsets from zoster vaccine would allow the funding of meningococcal B vaccine to proceed when it otherwise wouldn't be possible, as the bundle is ranked at s9(2) while one of the individual meningococcal B vaccine proposals was ranked s9(2)(b) and the other s9(2)(b)(ii), (s9(2) and s9(2)) the childhood vaccine proposal s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j)

- If this proposal is not approved, the current price of s9(2) per dose would remain in effect unless a price reduction was negotiated, either through direct contracting or a future RFP process.

Factors for Consideration

This paper sets out Pharmac staff's assessment of the proposal using the Factors for Consideration in the Operating Policies and Procedures. Some Factors may be more or less relevant (or may not be relevant at all) depending on the type and nature of the decision being made and, therefore, judgement is always required. The Decision Maker is not bound to accept Pharmac staff's assessment of the proposal under the Factors for Consideration and may attribute different significance to each of the Factors from that attributed by Pharmac staff.

We have addressed the factors separately for each medicine included in the multiproduct proposal.

Footnotes

[1] The person receiving the medicine or medical device must be an eligible person.
[2] The current Māori health areas of focus are set out in Pharmac's Te Whaioranga Strategy.
[3] Government health priorities are currently communicated to Pharmac by the Minister of Health's Letter of Expectations.
[4] Pharmaceutical expenditure includes the impact on the Combined Pharmaceutical Budget (CPB).
[5] Please note Pharmac's Factors for Consideration schematic currently does not explicitly refer to the health needs of family, whānau and wider society, but this factor should be considered alongside those depicted in the schematic.

Meningococcal B multicomponent vaccine (Bexsero) for immunisation against meningococcal B infection

Need

Background

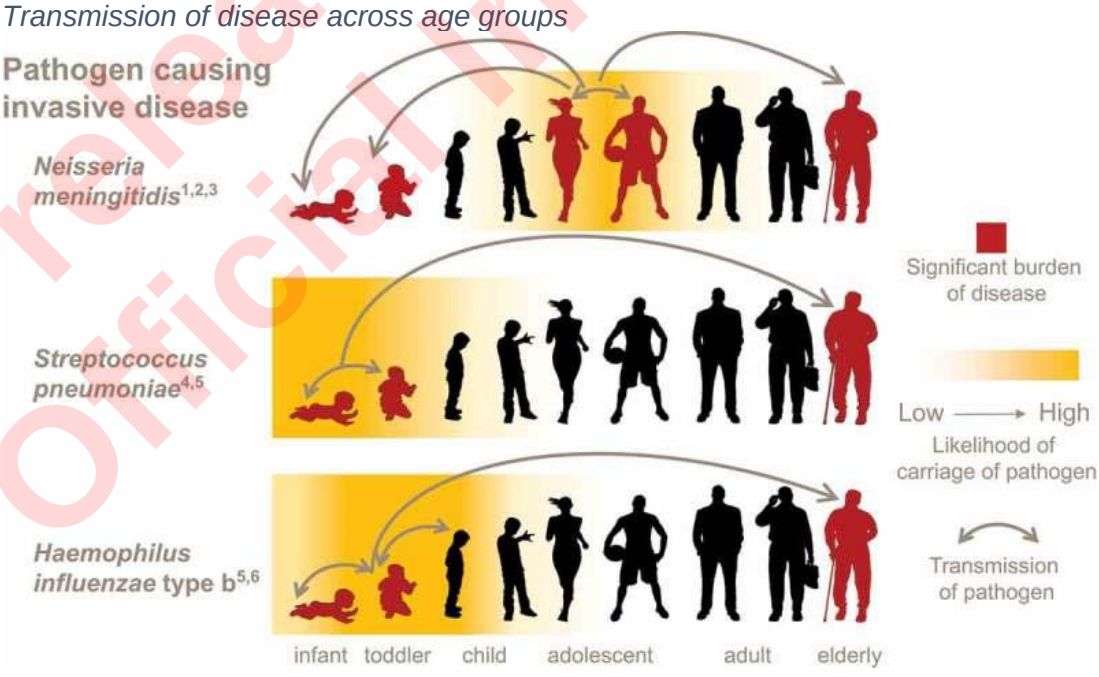
Disease/illness

Meningococcal disease is caused by the *Neisseria meningitidis* bacterium. Meningococcal bacteria are commonly carried in the nose and throat, and do not usually cause disease. Carriage rates are highest in teenagers and young adults but children under five years of age have the highest rates of meningococcal disease. Occasionally a person who is carrying the bacterium may develop severe (invasive) disease such as meningitis (inflammation of the membranes around the brain), septicaemia (blood infection) or pneumonia (lung infection). The bacterium can be spread from those who carry the bacterium without being infected (carriers), or from people with meningococcal disease, to other people by coughing, sneezing or contact with saliva.

Even when meningococcal disease is diagnosed and treated early, 10% to 20% of affected people may die. People who survive meningococcal disease may have long term consequences, including skin scarring, amputation of limbs and extremities, hearing loss, seizures or brain injury. On average in New Zealand, meningococcal group B causes around two-thirds of meningococcal disease each year. The remaining meningococcal cases each year are caused by other meningococcal groups.

Children under 5 years of age, adolescents and elderly people have the highest burden of meningococcal disease. The figure below shows how the carriage and transmission of meningococcal disease differs from other common pathogens. Carriage is highest in adolescents and young adults around the age of 20 years. They are responsible for the transmission of meningococcal disease to the most vulnerable groups in the community, infants and the elderly.

Transmission of disease across age groups

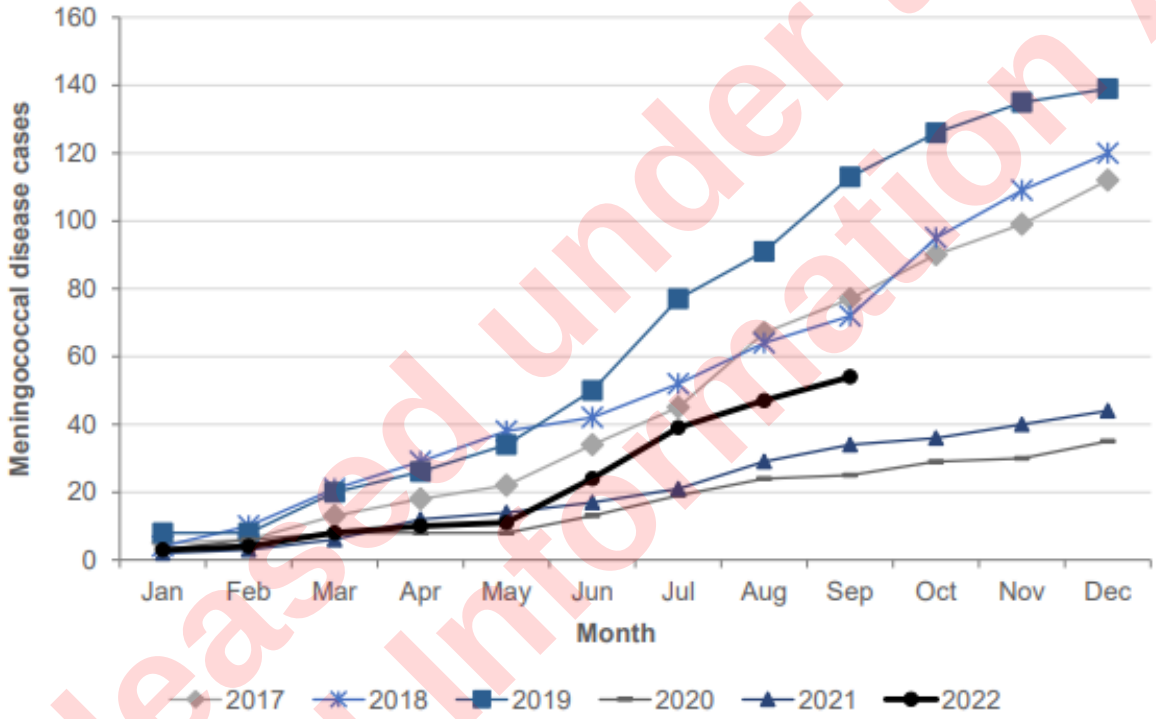


Source: Vetter et al. 2016.

Historically, the incidence of meningococcal disease in New Zealand has been predominantly caused by meningococcal serogroups B and C, although W and Y have increased in recent years. Groups W and Y have accounted for more cases than C since 2017. Mortality and morbidity associated with meningococcal C and W is higher than that associated with meningococcal B.

Meningococcal disease is a notifiable disease in New Zealand, meaning all cases are mandatorily reported to a Medical Officer of Health, via automated reporting of positive laboratory results and/or clinician notification, compiled and reported by the Institute of Environmental Science and Research (ESR). The graph below shows that the total number of meningococcal cases of all groups has been higher in 2022 than for the same period in 2020 and 2021, but is not as high as seen in 2017-2019.

Cumulative number of meningococcal cases by month, 1 January 2017 to 30 September 2022.



Source: Public health surveillance | ESR

Of the 54 cases notified to ESR from 1 January to 30 September 2022, the meningococcal group was identified in 44 cases. 36 of these were group B, five were group Y and three were group W. The table below shows that cases in 2022 to September have been geographically dispersed throughout the country, but have been predominately group B.

Number of meningococcal cases by group and district, 1 January to 30 September 2022

District	Group					Group unknown[1]	Not lab confirmed	Total
	B	W	Y	C	E			
Northland	3	0	0	0	0	1	0	**4**
Waitemata	5	0	0	0	0	0	0	**5**
Auckland	1	1	0	0	0	0	0	**2**
Counties Manukau	2	0	0	0	0	1	2	**5**
Waikato	3	0	0	0	0	0	0	**3**
Lakes	3	0	0	0	0	1	0	**4**
Bay of Plenty	4	1	1	0	0	0	1	**7**
Tairāwhiti	0	0	0	0	0	2	0	**2**
Taranaki	0	0	0	0	0	0	0	**0**
Hawke's Bay	0	0	0	0	0	0	0	**0**
Whanganui	2	0	0	0	0	1	0	**3**
MidCentral	0	0	0	0	0	0	0	**0**
Hutt Valley	1	0	0	0	0	0	0	**1**
Capital & Coast	2	0	0	0	0	0	0	**2**
Wairarapa	2	0	0	0	0	0	0	**2**
Nelson Marlborough	2	0	1	0	0	0	0	**3**
West Coast	0	0	0	0	0	0	0	**0**
Canterbury	3	1	0	0	0	0	0	**4**
South Canterbury	0	0	1	0	0	0	0	**1**
Southern	3	0	2	0	0	1	0	**6**
Total	**36**	**3**	**5**	**0**	**0**	**7**	**3**	**54**

[1] Includes non-groupable samples, and laboratory-confirmed cases where a sample was not received at ESR.

Source: Source: Public health surveillance | ESR

Availability and suitability of existing treatments

s9(2)(b)(ii), s9(2)(ba)(i) and s9(2)(j) [redacted]

Bexsero was funded from July 2021 for small sub-populations of patients considered to be at high risk. Up to two or three doses (depending on age at immunisation) and a booster every five years are funded for patients pre- and post-splenectomy and those with functional or anatomic asplenia, HIV, complement deficiency (acquired or inherited), or pre- or post-solid organ transplant; up to two or three doses (depending on age at immunisation) for close contacts of meningococcal cases, bone marrow transplant patients and for patients following immunosuppression (due to steroids or other immunosuppressive therapy must be for a period of greater than 28 days).

There are also two vaccines that protect against the meningococcal groups ACW and Y approved by Medsafe: Menactra (supplied by Sanofi) and Nimenrix (supplied by Pfizer). Nimenrix is currently only supplied to the private market in New Zealand.

Of note, there is no single vaccine available that covers all relevant strains of meningococcal disease (ie, A, B, C, W, and Y).

Since 2014, the Menactra brand of meningococcal ACWY vaccine has been funded for small sub-populations of patients considered to be high-risk. Access was widened from December 2019 for adolescents and young adults in close living situations. Menactra is currently not funded across any age group under the National Immunisation Schedule.

For the high-risk populations, up to three doses and a booster every five years are funded for patients pre- and post-splenectomy and those with functional or anatomic asplenia, HIV, complement deficiency (acquired or inherited), or pre- or post-solid organ transplant; one dose for close contacts of meningococcal cases; and two doses for bone marrow transplant patients and for patients following immunosuppression (due to steroids or other immunosuppressive therapy must be for a period of greater than 28 days).

One dose is funded for individuals who are entering into close living situations (specifically boarding school hostels, tertiary education halls of residence, military barracks, or prisons), and a catch-up programme for this group of individuals was in place until 30 November 2021. However, staff note that while prisons are included in the criteria, young people incarcerated in Oranga Tamariki Youth justice residences are not included. There are five youth justice residences, housing up to a total of 155 young people from 10 to 17 years of age. In addition to youth justice residences, there may be an unmet health need in a number of other situations exposing young people such as large student flats or crowded households. We will seek expedited clinical advice about widened access options for close living situations.

In meningococcal outbreak situations, the usual response to prevent ongoing transmission of the bacterium is to provide antibiotic chemoprophylaxis with oral antibiotics ciprofloxacin and rifampicin (and vaccine if appropriate) to those most at risk, ie close contacts of cases.

Health need of others

Meningococcal bacteria are transmitted from person to person through aerosol droplets, respiratory secretions and saliva, so there is risk to family or whānau members of contracting the disease and it may spread through the household and community.

The short-term impact on informal caregivers, family, and whānau is similar to that of any other acute medical condition.

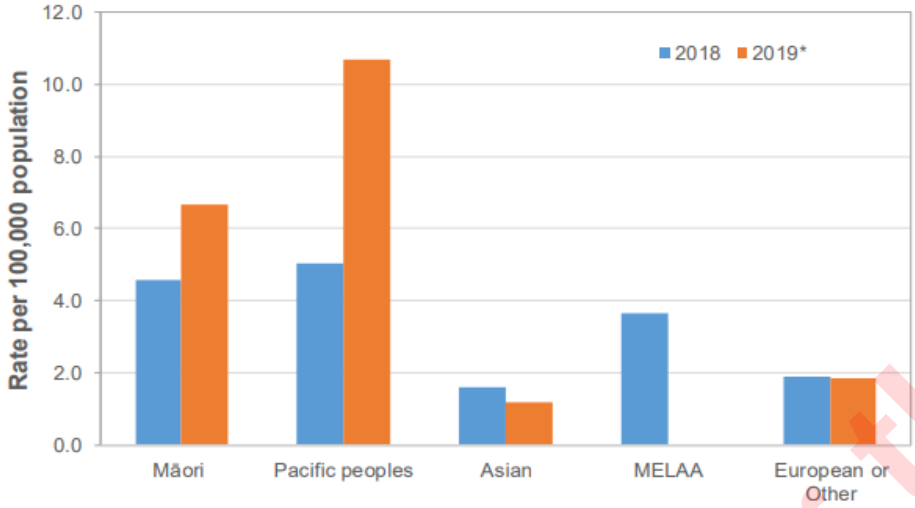
In the longer term, having to support affected cases, especially children, may affect the health of other people including informal caregivers, family, whānau. Many of the sequelae of meningococcal disease would be likely to create a burden on caregivers, to the point that they reduce the health-related quality of life of family and whānau.

Impact on Māori health areas of focus and health outcomes

Meningococcal disease is not one of the Hauora Arotahi, Māori health areas of focus, identified by whanau Māori and described in Te Whaioranga, Pharmac's Māori responsiveness strategy.

Rates of meningococcal disease are higher in Māori than in European or other populations (excepting Pacific Peoples), as shown in the figure below

*Meningococcal disease notification rates by ethnicity, 2018-2019**



*Cases reported up to 30 September 2019 only. Annualised rate using quarter 1-3 notifications. MELEAA – Middle Eastern/Latin American/African.

Risk factors for infectious diseases generally include lower socioeconomic status and over-crowded living conditions. Household crowding is an important risk factor for meningococcal disease, independent of ethnicity.

Any other populations experiencing health disparities

Meningococcal disease rates are typically higher in Pacific people compared to the total population and other ethnic groups. From January to August 2019, Pacific people had the highest Men ACWY disease rate (6.7 per 100,000) of all ethnic groups.

Is the disease/illness a government health priority

Meningococcal disease is a government health priority under infectious diseases and immunisation is a preventative population health approach.

Health Benefit

Treatment under consideration

Health benefits to the person

Bexsero provides active immunisation against invasive disease caused by *N. meningitidis* group B strains in individuals from two months of age.

This proposal would be expected to reduce the overall incidence, morbidity and mortality of meningococcal group B disease through a reduction in the incidence of meningococcal B disease.

Health benefit to others

Bexsero provides direct individual protection against meningococcal B infection but there is no evidence of herd immunity effects at this time.

Consequences for the health system

The infant dosing schedule consists of three doses which would be given at the current childhood immunisation programme at the 6 week, 2 month and 12 month visits. The catch-up doses for children and those in close living situations would require extra immunisation visits which would result in additional work for vaccinators and increased vaccination claim costs for the Ministry of Health.

Meningococcal B vaccination would reduce meningococcal-associated hospitalisation and requirement for therapy associated with long term sequelae of meningococcal infections.

PTAC /Specialist Advisory Committee View

Our clinical advisors, the Pharmacology and Therapeutics Advisory Committee (PTAC) and the Immunisation Subcommittee of PTAC, reviewed a funding application for meningococcal B vaccine in May 2018 and recommended funding for a range of different patient groups in March 2019, including:

- Close contacts of cases (medium priority)
- High risk immunocompromised people (high priority)
- Entrants to close living situations (13 to 25 years), with or without catch-up (high priority)
- Infant immunisation schedule (low priority).

More information, including links to the records of the relevant PTAC and Subcommittee meetings which include a detailed analysis of the clinical trial evidence about health benefits, can be found in the Application Tracker record for meningococcal group B vaccine.

Advisor Conflicts of Interest

No relevant conflicts of interest have been declared by any of the clinical advisors who contributed to the above advice.

Suitability

Bexsero is a suspension for injection, supplied in a prefilled syringe. It is administered by deep intramuscular injection, either in the anterolateral aspect of the thigh in infants or in the deltoid muscle region of the upper arm in older recipients.

Bexsero is approved by Medsafe for active immunisation against invasive disease caused by *N. meningitidis* group B strains. It is approved for use in individuals from two months of age and older.

Bexsero is considered to be a reactogenic vaccine, meaning that some people may have a reaction at the injection site or infants may develop a fever after vaccination. This could typically be managed by giving infants paracetamol prophylactically prior to immunisation. Despite this, the Immunisation Subcommittee considered that the use of Bexsero could result in an increase in Emergency Department presentations by some parents seeking care for their child with fever following immunisation, however it still recommended that Bexsero be funded.

Costs and Savings

Health related costs and savings to the person

Vaccines are listed on the Pharmaceutical Schedule at no price or subsidy as they are purchased by Pharmac and supplied to vaccinators free of charge. Te Whatu Ora pays vaccinators an immunisation service fee, so the patient should not incur any costs from vaccination.

Health related costs and savings to the family, whānau and wider community

As noted above in the Health need of others section, informal caregivers, family and whānau of people who have long term sequelae from meningococcal infection may have an increased burden of care. This may result in additional costs incurred for the management of consequences from the long-term sequelae of infection.

Cost and savings to Pharmaceutical expenditure

Although staff have successfully negotiated a significant price reduction for meningococcal B vaccine, from s9(2)(b)(ii), s9(2)(ba)(i) per dose through the bundle proposal, the budget impact analysis estimates that this proposal would result in a cost to the CPB of s9(2)(b) million (5 year NPV, 8%).

The proposed term of subsidy and delisting protection for meningococcal B vaccine extends beyond the start of the 2022 Vaccine RFP supply period, so meningococcal B vaccines have not been included in the RFP, meaning there would be no further price reductions as a result of the RFP.

Distribution of vaccines is separately contracted for by Pharmac and not included in the assessment.

Whilst vaccines can be administered in hospitals, for the purposes of this assessment it is assumed that all vaccinations would be given in the community. The assessment accounts for a full vaccination course for every child and eligible young adults, using vaccines pre-purchased by Pharmac. Whether the vaccine is administered in the community or hospital has no bearing on the budget impact to the CPB.

Costs and savings to the rest of the health system

Te Whatu Ora pays vaccinators an immunisation service fee for each funded immunisation event. The immunisation subsidy is $27.84. There would be no additional subsidy payable for infant immunisations as these would be given along with other scheduled childhood immunisations, but there would be additional immunisation claims for the catch-up doses for children between 12 months and five years of age, as well as young adults in close living circumstances. Pharmac staff estimate this would incur a cost to the Te Whatu Ora of $10.2 million (5-year NPV, 8% discount rate). If the vaccine was administered in hospital, there would be no immunisation service fee paid.

Cost-Effectiveness

Meningococcal B vaccine was previously ranked at number s9(2) for infants and s9(2) for close living situations on the options for investment list, based on the previous pricing proposal that had been received.

The savings from the bundle proposal have been incorporated into the cost effectiveness of the multiproduct proposal, which is currently ranked at number s9(2) on the Options for Investment list (September 2022).

Consultation responses relating to meningococcal B vaccine

Consultation responses were supportive of the proposal to fund meningococcal B vaccine, with 79 responses received. However, many responses also included requests for wider access to meningococcal B vaccine for a range of different age groups and wider access for meningococcal ACWY vaccine.

Summaries of what Pharmac staff believe are the significant matters raised in these responses are provided below. For the full response, please refer to Appendix Three.

Theme	Pharmac Staff Comment
Support for the proposal. In particular it was noted that: • Meningococcal disease has an inequitable impact on Māori and Pacific children • Effective meningococcal vaccination of infants has the potential to eliminate ethnic inequalities in meningococcal disease in New Zealand • The funding of this vaccine would save Māori and Pacific lives	We acknowledge the significant support for this proposed change and the importance of meningococcal vaccination for children and adolescents.
Requests for further widened access for a range of additional groups: • All people up to 16 years of age • All people 13-25 years of age • Ongoing funding for all children under 5 years of age • Longer time for the infant catch-up programme • Widen the definition of close living situations to include large household situations	This proposal includes all the currently unfunded groups that are on the Options for Investment list. At its March 2019 meeting the Immunisation Advisory Committee considered that meningococcal B epidemiology shows the bimodal burden of disease with peaks for children under five years and people 15-20 years of age. The committee considered that although there is evidence of herd immunity effects for meningococcal ACWY vaccines, there is no documented herd immunity effect for meningococcal B vaccination. Without herd immunity effects, vaccination needs to be targeted to those most at risk from meningococcal disease. We would welcome a funding application with supporting evidence for widened access to additional groups. The duration of the infant catch-up programme was set in consultation with the National Immunisation Programme, who advised that the proposed period would be required to ensure that children over 15 months of age would still be eligible for a catch-up dose at their 4 year immunisation visit. We are open to considering an extension of the catch-up in the future if good immunisation coverage rates of children under 5 years have not been achieved.

Theme	Pharmac Staff Comment
Requests to widen access for meningococcal ACWY vaccine as well • Infant immunisation programme • All people 13-25 years of age, regardless of their living situations.	A number of proposals for widened access to meningococcal ACWY vaccine are currently on the Options for Investment list. We would like to fund these, subject to available budget. These proposals can be viewed on the Application Tracker and include: • Adolescents at 14 years of age • Adolescents at 14 years of age with catch up for 5 to 21 years • Adolescents at 14 years of age with catch up for 13 to 21 years • Children at 1 year of age • Children at 1 year of age with catch up for 1 to 4 years
Request to fund meningococcal B earlier, from February 2023 to allow for vaccination of tertiary students before they enter halls of residence from mid-February.	We acknowledge that an earlier start date would provide earlier protection to eligible people, however the 1 March 2023 start date allows time for the supply of the large quantities of vaccine required to support the proposal.
Requests for meningococcal B to be available for administration by Pharmacists to reduce barriers to access and free up time for GPs and nurses.	As with most other funded vaccines, pharmacist vaccinators would not be able to administer this funded vaccine at this time. Significant changes would be required to the current funding and distribution process to allow pharmacists to administer all funded vaccines. We acknowledge the importance of reducing barriers to access and continue to discuss with Te Whatu Ora options for changes to the funding and distribution process and implementation of the immunisation programme that would allow pharmacists to administer all funded vaccines in the future.
Some respondents offered suggestions for Pharmac to work with the Te Whatu Ora National Immunisation Programme for smooth implementation, including ensuring that Māori and Pacific people are given priority in the implementation plans.	Te Whatu Ora would be responsible for the implementation of any funding decision through the National Immunisation Programme and Pharmac staff work very closely with Te Whatu Ora staff to ensure the success of the Programme. We will share the implementation suggestions received in consultation feedback with Te Whatu Ora and continue to work closely and collaboratively to support implementation of immunisation programmes.
The Public Health Agency noted that meningococcal disease has an inequitable impact on Māori and Pacific children. In addressing this it is important to improve access to primary care and childhood immunisation services. Universal access supports equity but targeted implementation is still needed to support equity. Time limits work against equity, noting a higher proportion of Māori and Pacific children are immunised later than their milestone due dates. The proposed close living situations do not include multi-generational or overcrowded households outside of formal institutions.	We acknowledge the concerns regarding Māori and Pacific children experiencing inequities in meningococcal disease. We will share the feedback about improving equity by targeted implementation for Māori and Pacific children with Te Whatu Ora, and continue to work closely and collaboratively to support implementation of immunisation programmes. We acknowledge that time limited programmes may work against equity, particularly where there are barriers to accessing health care or delays in routine immunisations. Pharmac uses time limited programmes in some circumstances, particularly where programmes are high volume or high value. Pharmac staff consider that further widening the close living situation criteria would best be assessed as a separate funding proposal and we will work with our clinical advisors to develop this.
One respondent expressed anti-vaccination views and regarded the proposal as criminal.	We note this feedback.

Changes in response to consultation feedback

No changes have been made to the proposed eligibility criteria for meningococcal B vaccine following consideration of the consultation feedback.

Zoster vaccine (Shingrix) for immunisation against zoster (shingles)

Need

Background

Disease/illness

Herpes zoster, commonly known as shingles, is a painful blistering rash caused by the same virus that causes chickenpox. Anyone who has previously had chickenpox may subsequently develop shingles, which tends to occur more often in older people. Shingles is more common and more severe in patients with poor immunity.

One in every three people can expect to suffer at least one attack of shingles in their lifetime. Particularly for older people, shingles and post-herpetic neuralgia can be very painful, prolonged and debilitating and may affect their ability to carry out simple daily activities, such as dressing and bathing.

Availability and suitability of existing treatments

Shingrix has been funded for immunisation against shingles for people who are 65 years of age since 1 August 2022. Two doses are required, given six months apart. It is supplied as two vials, one containing a single dose of the zoster antigen, which needs to be reconstituted with the adjuvant suspension contained in the second vial. An adjuvant is a substance used to enhance the immune response to an antigen.

Shingrix may be administered at the same time as the unadjuvanted seasonal influenza vaccine. It can also be administered at the same time as COVID-19 vaccines, except Nuvaxovid (supplied by Novavax) which also contains an adjuvant.

Shingrix is a recombinant vaccine that is approved by Medsafe for the prevention of herpes zoster (shingles) and post-herpetic neuralgia in people 50 years of age or older and people 18 years of age or older who are at increased risk of shingles. It may be given to people who are immunocompromised.

Shingrix was funded in August 2022 when the previously funded Zostavax was discontinued by the supplier. Zostavax was a live attenuated vaccine, which made it contraindicated in individuals who are immunocompromised. Careful pre-administration screening was required by vaccinators to ensure the live zoster vaccine was suitable for each person.

Health need of others

Both herpes zoster and post herpetic neuralgia impact patient's family and whānau, with patients and whānau reporting feeling isolated and having reduced communication during the time of illness (Lukas et al. Z Gesundh Wiss. 2012;20:441-51). Some patients do not recover enough to return to independent living, resulting in significant carer burden for caregivers of patients including partners, relatives, whānau and friends (Scott et al. Vaccine. 2006;24:1308-14). Patients may also not be able to continue to work, which can further impact burden on partners and family.

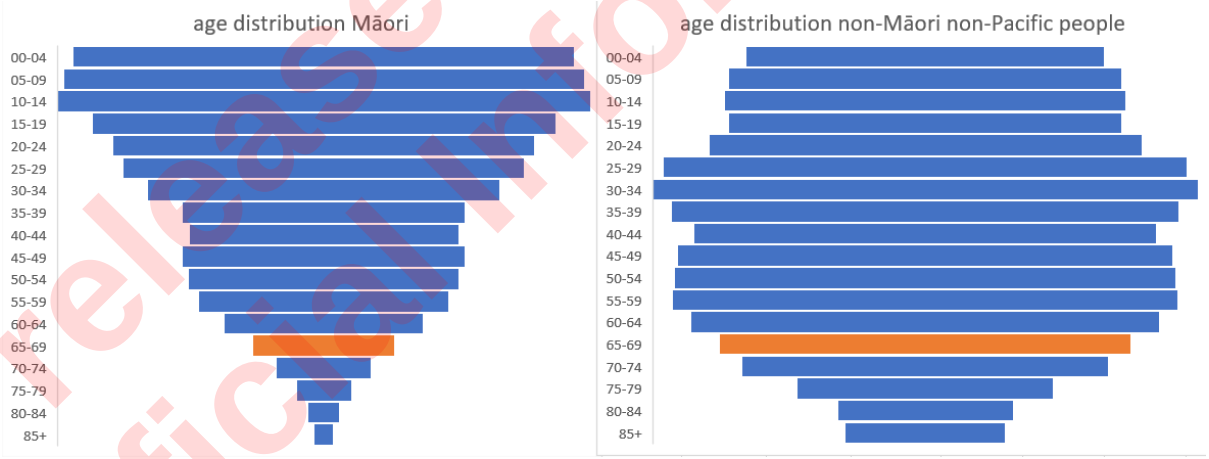
Impact on Māori health areas of focus and health outcomes

People living with the long-term conditions diabetes mellitus and COPD have an increased risk of complications from herpes zoster. Māori and Pacific peoples also have a higher incidence of these diseases compared to non-Māori and non-Pacific people in New Zealand and their associated comorbidity. However, Pharmac staff also note that as there is limited data on herpes zoster related hospitalisations for Māori and Pacific people, the true burden from severe herpes zoster infection in these populations is unknown.

There is data on the burden of herpes zoster cases in primary care reporting a slightly lower incidence of herpes zoster in Māori compared with other ethnicities, with factors such as varicella zoster virus (chickenpox) primary exposure in childhood and socioeconomic factors not appearing to be linked to this lower incidence (Turner et al. BMJ Open. 2018;8:e021241). However, the Immunisation Advisory Committee (May 2022) has considered that reduced access to primary healthcare and underdiagnosis in the Māori population may impact reported incidence rates; this would imply reported lower incidence of herpes zoster in Māori in primary care could falsely understate true Māori herpes zoster burden.

In May 2022, the Immunisation Advisory Committee noted that Māori and Pacific people have a lower life expectancy than non-Māori and non-Pacific people, where Māori males and females aged 50 years have 5.7 and 6.2 fewer expected number of years of life remaining at age 50 compared with non-Māori males and females respectively (calculated from New Zealand period life tables: 2017–2019).

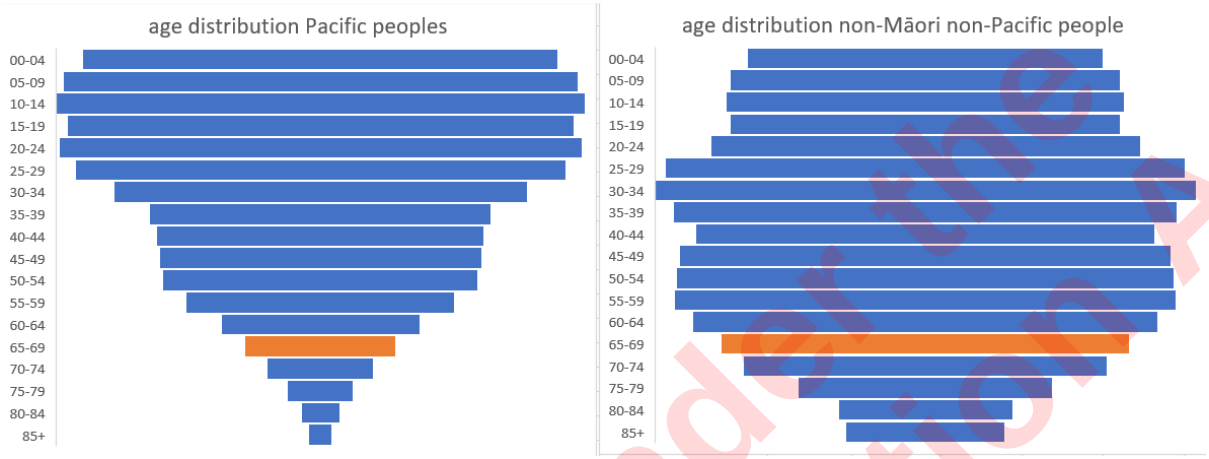
Pharmac staff note that the population age structure of the combined Māori and Pacific peoples' populations is younger compared to that of the non-Māori non-Pacific population's age structure. This means a greater proportion of their respective population die before reaching 65 years of age, leaving a smaller proportion of their population that might benefit from herpes zoster vaccination under the current access criteria. The figure below shows the age distribution for Māori compared with non-Māori, non-Pacific people.



In addition, reflecting their lower life expectancies overall, the life expectancies for Māori and Pacific peoples aged 65 years are 3.3 to 4 years less than non-Māori and non-Pacific people of the same age (Statistics NZ 2021 period life tables 2017-9). This means Māori and Pacific recipients of a herpes zoster vaccine would likely gain less benefit, in terms of the full duration of vaccine protection, than non-Māori non-Pacific recipients, because they are at an increased risk of dying at a younger age.

Any other populations experiencing health inequities

As described above, Pacific peoples have a higher incidence of diabetes mellitus and COPD compared to non-Māori and non-Pacific people in New Zealand. Pacific peoples also have a younger population age structure and lower life expectancy overall compared to the non-Māori and non-Pacific people in New Zealand, meaning they would gain less benefit, in terms of the full duration of vaccine protection. The figure below shows the age distribution for Pacific people compared with non-Māori, non-Pacific people.



Is the disease/illness a Government health priority

While immunisation against herpes zoster does not specifically fall into the overarching Government health priorities, both treatments for and immunisation to prevent infectious diseases are considered priorities.

Health Benefit

Treatment under consideration

Health benefits to the person

In May 2022, the Immunisation Advisory Committee considered that the majority of the studies it reviewed were consistent in reporting high levels of vaccine efficacy for the recombinant vaccine, regardless of age, and sustained over time. The Committee also noted that maximum benefit was gained from receiving two doses of Shingrix, and that vaccine effectiveness was above 90% for protection against PHN and other HZ related complications for most age groups.

The Committee considered that there was good evidence that Shingrix is likely a more effective vaccine than the previously funded Zostavax. The duration of benefit from Shingrix extends to at least eight to ten years post-vaccination, compared to Zostavax where immunity declined within three to four years.

Health benefit to others

Our clinical advisors considered that the increased effectiveness of Shingrix against PHN and HZ related complications compared to Zostavax would provide a benefit to family and whānau of patients with HZ in that there would be a reduction caregiver burden.

Consequences for the health system

Shingles vaccine is administered predominately in primary care. The two-dose course for Shingrix requires an additional immunisation appointment compared to the previously funded Zostavax, which was given as a single dose. Shingrix may be administered at the same visit as other vaccines scheduled for administration at 65 years of age (influenza and Tdap [diphtheria, tetanus and pertussis] vaccines) which would reduce the number of immunisation service subsidy claims paid by the Ministry of Health.

Our clinical advisors considered that funding Shingrix would reduce the health system impact of HZ related complications and may also lessen some of the extra impacts due to COVID-19 infection. They did not consider that funding Shingrix would create any significant change in health-sector expenditure other than for direct treatment costs.

PTAC /Specialist Advisory Committee View

Pharmac first sought clinical advice about live attenuated zoster vaccine in August 2014, when PTAC recommended Zostavax be funded with a medium priority. Further advice was sought from:

- the Immunisation Subcommittee in February 2015 (now the Immunisation Advisory Committee), which recommended it be funded with no priority given.
- the Pharmacology and Therapeutics Advisory Committee (PTAC) in August 2015, which recommended that it be funded with a medium priority for vaccination at 65 years of age.
- PTAC in February 2016, which recommend that it be funded with a medium priority for people 65 years of age with no catch-up programme, and with a low priority for people 65 years of age with a two-year catch-up programme for people between 65 and 80 years of age.

Pharmac received a funding application specifically for recombinant zoster vaccine (Shingrix) in April 2022. Clinical advice was sought on the suitability of funding Shingrix when Zostavax was discontinued by the supplier. We sought advice from the Immunisation Advisory Committee in May 2022, which considered that there would be a high unmet health need, especially for older age groups at risk of HZ if zoster vaccine was no longer available in New Zealand. The Committee considered that Shingrix would be an appropriate alternative to Zostavax if it was discontinued. The Committee also recommended that Shingrix be funded with a high priority for all people 50 to 64 years of age, and with a low priority for people of Māori or Pacific ethnicity 60 years of age or over – where members had considered that, if Shingrix were funded in New Zealand, that it would be appropriate to have Māori and Pacific people access the vaccine at an earlier age (given lower life expectancy), their access age lowered relative to their reduced life-expectancy at the age of vaccination. The Committee considered that people who had already been vaccinated with Zostavax would benefit from revaccination with Shingrix after three to five years following the previous Zostavax dose, to address the waning effect from Zostavax.

Advisor Conflicts of Interest

s9(2)(a) [redacted]
s9(2)(a) [redacted]

Suitability

Shingrix is supplied as two vials, one containing a single dose of the recombinant varicella zoster virus glycoprotein E (active ingredient) in a lyophilised form which needs to be reconstituted using the other vial containing a single dose of the Adjuvant System AS01B in suspension. It is administered by deep intramuscular injection, preferably in the deltoid muscle.

Shingrix is approved by Medsafe for the prevention of herpes zoster and post-herpetic neuralgia in adults 50 years of age and older, and in adults 18 years of age or older at increased risk of herpes zoster.

Costs and Savings

Health related costs and savings to the person

Vaccines are listed on the Pharmaceutical Schedule at no price or subsidy as they are purchased by Pharmac and supplied to vaccinators free of charge. Te Whatu Ora pays vaccinators an immunisation service fee, so the patient should not incur any costs from vaccination.

Health related costs and savings to the family, whānau and wider community

As noted above in the Health need of others section, some patients do not recover enough from herpes zoster or post herpetic neuralgia to be able to return to independent living. This can result in significant carer burden, which result in additional health related costs incurred by family or whānau.

Cost and savings to Pharmaceutical expenditure

Staff have successfully negotiated a significant price reduction from the initial listing price for Shingrix, from s9(2)(b)(ii), s9(2)(ba)(i) and per dose through the bundle proposal. As such, we estimate that this proposal would result in savings to the CPB of s9(2)(b)(ii), s9(2) (5 year NPV, 8%).

The proposed term of subsidy and delisting protection for shingles vaccine extends beyond the start of the 2022 Vaccine RFP supply period, so shingles vaccines has not been included in the RFP, meaning there would be no further price reductions as a result of the RFP.

Distribution of vaccines is separately contracted for by Pharmac and not included in this assessment.

Whilst vaccines can be administered in hospitals, for the purposes of this assessment it is assumed that all vaccinations would be given in the community. The assessment accounts for a full vaccination course for eligible adults, using vaccines pre-purchased by Pharmac. Whether the vaccine is administered in the community or hospital has no bearing on the budget impact.

Costs and savings to the rest of the health system

Te Whatu Ora pays vaccinators an immunisation service fee for each funded immunisation event. The immunisation subsidy is $27.84 or $19.54 if zoster is administered at the same time as influenza vaccine. Pharmac staff estimate that the average immunisation subsidy

paid for zoster vaccination course is $50.70. As Shingrix is already listed in the Pharmaceutical Schedule, there would be no additional immunisation subsidy payable. Overall, costs of $10.2 million would be incurred by Te Whatu Ora as part of this proposal, to fund the increased immunisation claim costs from increased vaccination events.

Cost-Effectiveness

Shingles vaccine was not ranked as a standalone proposal on the Options for Investment list as it is already funded for people who are 65 years of age, and this proposal would maintain the intent of the current listing for the same population while reducing the cost through a negotiated price reduction.

The savings from the Shingrix proposal have been incorporated into the cost effectiveness of the multiproduct proposal for zoster and meningococcal B vaccines, which is currently ranked at numbe[s9(2)]on the Options for Investment list (September 2022).

Consultation response regarding zoster vaccine

Consultation responses were supportive of the proposal to fund zoster vaccine, with 20 responses received. Many respondents also requested wider access for several specific groups.

Summaries of what Pharmac staff believe are the significant matters raised in these responses, and in previous enquiries to Pharmac considerable in number, are provided below. For the full response, please refer to Appendix Three.

Theme	Pharmac Staff Comment
Most responders were supportive of the proposal.	We acknowledge the support from most respondents for the proposed change.
Requests for further widened access for a range of additional groups: • All people over 65 years of age • People over 65 years of age who were not able to be vaccinated with Zostavax because they were immunocompromised • Māori and Pacific people from the earlier age of 55 years • People from 18 years of age who are immunocompromised • People over 65 years of age who missed their zoster vaccination at 65 years of age while access to immunisation services or health care was reduced during the COVID-19 pandemic	Our clinical advisors have recommended wider funding of Shingrix for a range of additional groups, including: • People from 50 to 64 years of age • People over 65 years of age who received Zostavax at least five years previously • Māori and Pacific peoples 60 years of age and over The proposals for people from 50 to 64 years of age and people over 65 years of age who have previously received Zostavax are currently on the Options for Investment list. We are still assessing the proposal for Māori and Pacific peoples 60 years of age and over. We are also assessing and seeking further clinical advice about other groups that may benefit from Shingrix, including: • People 18 years of age and over who are immunocompromised • People over 65 years of age who missed their zoster vaccination at 65 years of age while access to immunisation services or health case was reduced during the COVID-19 pandemic • people over 65 years of age who were immunosuppressed and could not be vaccinated with Zostavax when they were 65 years of age.

Theme	Pharmac Staff Comment
Limiting eligibility to people who are 65 years of age can disadvantage people who do not engage frequently with the health system.	We acknowledge that time limited programmes may work against equity, particularly where there are barriers to accessing health care or delays in routine immunisations. Pharmac uses time limited programmes in some circumstances, particularly where programmes are high volume or high value.
One respondent expressed anti-vaccination views and regarded the proposal as criminal.	We note this feedback.

Changes in response to consultation feedback

No changes have been made to the proposed eligibility criteria for shingles vaccine following consideration of the consultation feedback.

We continue to assess wider funding of Shingrix for additional patient groups:

- people from 50 to 64 years of age
- people aged over 65 years who have received Zostavax at least 5 years previously
- Māori and Pacific peoples aged 60+ years
- people aged 18+ years who are who are immunosuppressed
- people over 65 years of age who missed their zoster vaccination at 65 years of age while access to immunisation services or health care was reduced during the COVID-19 pandemic
- people over 65 years of age who are immunosuppressed and could not be vaccinated with Zostavax when they were 65 years of age.

Consultation and Consumer Engagement

Consumer engagement

Direct consumer engagement regarding this specific proposal has not occurred. However, we have heard from patient support groups and individual consumers have provided feedback to consultation.

Consultation

Section 70(a) of the Pae Ora (Healthy Futures) Act 2022 (the Act) requires Pharmac to consult, when it considers appropriate to do so, on matters that relate to the management of pharmaceutical expenditure with any sections of the public, groups or individuals that, in the view of Pharmac, may be affected by decisions on those matters.

Accordingly, a consultation letter was circulated on 25 October 2022 to all suppliers and other parties that, in the view of Pharmac, may be affected by the recommendations contained in this paper. The consultation was distributed to clinicians, consumer advocacy groups, clinical groups and other parties who are interested in immunisations.

The consultation letter, the distribution list, and all responses received by 8 November 2022 are attached as Appendix Three.

Legal Advice

Where necessary, management will obtain legal advice on issues such as whether any proposal is consistent with Pharmac's legislative and public law obligations, including those which may have specific relevance to the particular proposal eg human rights implications of a proposal. If the Board considers that further legal advice is required on any issue, this should be communicated to management in advance of the Board meeting. Management will then obtain the required advice.

Legal Advisors' View

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Impact for Māori

The process for development of this proposal would ideally have seen earlier inclusion of Māori perspectives. This is something Pharmac is looking to strengthen ahead as part of improving how we give effect to Te Tiriti.

Meningococcal B vaccine

As noted in the Impact on Māori health areas of focus and health outcomes for meningococcal vaccine, the rates of meningococcal disease are higher in Māori than European and other populations, apart from Pacific peoples. Half of invasive meningococcal disease cases in 2022 to-date have occurred in Māori and Pacific children under five years of age. Māori children who contract invasive meningococcal disease are twice as likely to die or experience sequelae than non-Māori children.

Zoster vaccine

As noted in the Impact on Māori health areas of focus and health outcomes for zoster vaccine, the population age structure of the Māori population is younger compared to that of the non-Māori, non-Pacific population's age structure. This means a greater proportion of the

s9(2)(b)(ii), [redacted]

population die before reaching 65 years of age, leaving a smaller proportion of the population that might benefit from herpes zoster vaccine under the current access criteria.

Equity Implications

As discussed under the Factors for Consideration, the funding of meningococcal B vaccine is anticipated to be equity enhancing because meningococcal disease rates are higher in Māori and Pacific people compared to non-Māori, non-Pacific people. The proposal to secure ongoing supply of shingles vaccine is not expected to have any direct impact on achieving equitable health outcomes.

Pharmac staff note that although the proposed funding would make vaccines available for the immunisation programme, Te Whatu Ora would be responsible for the implementation of any funding decision through the National Immunisation Programme. A successful implementation programme could strongly influence equity of access by ensuring services are targeted to priority groups within the overall funded population.

Financial Implications

The financial implications of this proposal are outlined in the Cost and Savings discussion under the Factors for Consideration section of this paper and in the Summary budget impact analyses assessment (Table 1) and in the individual budgetary impact assessments located in Appendix One.

Risk Implications

Risks

Description	Mitigation
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Implementation and Communication

Section 70(b) of the Act requires Pharmac to take measures to inform the public, groups and individuals of Pharmac's decisions concerning the pharmaceutical schedule. Accordingly, if the recommendations contained in this paper are adopted, Pharmac staff will take the following measures to inform the public, groups and individuals of that decision:

- Suppliers would be notified directly, and the notification of a decision shared with the supplier prior to release.
- The National Immunisation Programme at Te Whatu Ora holds responsibility for implementing the National Immunisation Schedule and monitoring immunisation rates. The Programme team will be notified by Pharmac staff following a decision, and further discussion at monthly meetings between Pharmac and the Programme would continue. Pharmac would work with Te Whatu Ora to communicate the notification.
- Media would be notified ahead of a published decision. There has been some media interest covering meningococcal cases and the consultation to widen access to meningococcal B vaccine.

Te Whatu Ora is responsible for implementation of this proposal through the National Immunisation Schedule. Pharmac staff would work closely with Te Whatu Ora to monitor current and forecast future uptake to inform vaccine purchasing.

Appendices

Appendix One: Individual budget impact analysis

Appendix Two: 5 October 2022 Letter of Agreement between GSK and Pharmac

Appendix Three: Consultation letter, responses, and distribution list.