Record of the Immunisation Advisory Committee Meeting held on 09 September 2022

This meeting was held virtually via Zoom

Immunisation Advisory Committee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) Specialist Advisory Committees 2021.

Note that this document is not necessarily a complete record of the Immunisation Advisory **Committee meeting**; only the relevant portions of the meeting record relating to Immunisation Advisory Committee discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

The Immunisation Advisory Committee may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or Specialist Advisory Committees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

Table of Contents

1. Attendance

Present	**Apologies**
Stephen Munn (Chair)	Sean Hanna
Edwin (Gary) Reynolds	
Elizabeth Wilson	
Giles Newton-Howes	
Karen Hoare	
Lance Jennings	
Michael Tatley	
Nikki Turner	
Osman Mansoor	
Stuart Dalziel	
Tony Walls	

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Pneumococcal 15-valent conjugate vaccine (PCV15) for prevention of pneumococcal disease in paediatrics and adults.	Medium Priority
• High dose quadrivalent influenza vaccine for people aged 65 years and over.	High Priority
• High dose quadrivalent influenza vaccine for Māori and Pacific people aged 60 years and over.	High Priority
• Quadrivalent influenza virus haemagglutinin, surface antigen, inactivated, prepared in cell cultures for persons aged ≥6 months to <65 years who have certain medical conditions	Medium Priority

that increase the risk of influenza disease complications.	
• Quadrivalent influenza virus haemagglutinin, surface antigen, inactivated, prepared in cell cultures for Māori and Pacific people aged ≥55 to <65 years.	Medium Priority
• Quadrivalent influenza virus haemagglutinin, surface antigen, inactivated, prepared in cell cultures for persons aged ≥65 years.	Cost neutral
• Quadrivalent influenza virus haemagglutinin, surface antigen, inactivated, prepared in cell cultures for persons aged ≥6 months to <3 years who have certain medical conditions that increase the risk of influenza disease complications.	High Priority
• DTPa-hepB-IPV-Hib - Vaccination of infants from six weeks of age against DTPa-hepB-IPV-Hib	Deferred

3. The role of Specialist Advisory Committees and records of meetings

3.1. This meeting record of the Immunisation Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and Specialist Advisory Committees 2021, available on the Pharmac website at https://pharmac.govt.nz/assets/2021-Specialist-Advisory-Committee-Terms-of-Reference.pdf. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

3.3. The Immunisation Advisory Committee is a Specialist Advisory Committee of Pharmac. The Immunisation Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Immunisation Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for Immunisation that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments of Immunisation that differ from the Immunisation Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

Pharmac considers the recommendations provided by both the Immunisation Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for Immunisation.

4. Record of Immunisation Advisory Committee meeting held Monday, 9 May 2022

4.1. The Advisory Committee reviewed and accepted the record of the Immunisation Advisory Committee meeting previously held on Monday, 9 May 2022.

5. Pneumococcal 15-valent conjugate vaccine (PCV15) for prevention of pneumococcal disease in paediatrics and adults

Application

5.1. The Committee reviewed the application from Merck Sharpe and Dohme (MSD) for Vaxneuvance pneumococcal 15-valent conjugate vaccine (PCV15) to be listed in the National Immunisation Schedule for the prevention of invasive pneumococcal disease (IPD) in paediatrics and adults.

5.2. The Committee noted that the supplier proposed PCV15 be funded for the same patient populations who are currently eligible for PCV10 or PCV13, and according to the same dose regimens.

5.3. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

5.4. The Committee **recommended** that the pneumococcal 15-valent conjugate vaccine (PCV15) could replace either PCV10 or PCV13 in the Pharmaceutical Schedule with a 2+1 dosing schedule for children under 5 years of age, a 3+1 dosing schedule for children at higher risk, and up to four additional doses for the currently funded high-risk groups, within the context of vaccines and immunisation, with a **medium priority**.

5.5. In making this recommendation, the Committee considered that:

5.5.1. There is a large burden and high health need from pneumococcal disease arising from consequences beyond IPD alone (ie due to non-invasive disease).

5.5.2. The impact of pneumococcal disease is high in people already experiencing health inequities (eg Māori and Pacific infants, and people living in areas of greater deprivation).

5.5.3. PCV15 likely provides comparable benefit to PCV13 at a population level and therefore would be considered interchangeable with PCV13, based on the immunogenicity data reviewed.

5.5.4. Immunogenicity outcomes for serotype 19A in the paediatric trials of PCV15 likely reflect adequate serotype coverage relative to that of PCV13, although the trials were designed for non-inferiority.

5.5.5. PCV15 would be suitable as a single funded pneumococcal conjugate vaccine for prevention of pneumococcal disease in the proposed populations including high-risk groups currently eligible to receive PCV13.

5.5.6. The timing and implementation of any change to the funded pneumococcal vaccine, surveillance by serotype and age, and established IPD thresholds for timely and reactive action would all be highly important in the context of pneumococcal disease.

Discussion

Māori Impact Statement

5.6. The Committee considered that Māori are disproportionately affected by IPD in terms of incidence and mortality, with a risk of IPD over three times higher than that for New Zealand Europeans. In August 2021, the Immunisation Subcommittee previously considered that Māori were over-represented in the serotype 19A cases that occurred in 2020 in children under five years of age. The Committee considered that it was not known, based on current data, whether a disproportionate number of cases of adults with serotypes 22F or 33F (the additional serotypes covered by PCV15 over PCV13) were Māori.

Background

5.7. The Committee noted that it has considered pneumococcal vaccines in recent years, that PCV10 is funded for unvaccinated individuals up to the age of 59 months inclusive, and that PCV13 is currently funded for high-risk children and for testing for primary immunodeficiency diseases. The Committee noted that:

5.7.1. In August 2021, the Immunisation Subcommittee considered surveillance data on the rising incidence of IPD serotype 19A in the context of overall decline of IPD and recommended that PCV13 be reintroduced into the Childhood Immunisation Schedule.

5.7.2. In February 2022, PTAC considered supplier correspondence in response to the Immunisation Subcommittee's August 2021 recommendation and supporting unpublished data.

5.7.3. The Immunisation Advisory Committee (previously the Immunisation Subcommittee) most recently considered the PCV13 vaccine in April 2022 including PCV supplier correspondence and considered that the evidence supported the Committee's August 2021 recommendation that the PCV13 vaccine be listed in the Pharmaceutical Schedule with a 2+1 dosing schedule for children under 5 years of age.

Health Need

5.8. The Committee noted that invasive pneumococcal disease (IPD) is associated with severe morbidity and mortality especially in children under five years of age, the elderly, and individuals with underlying conditions. The Committee noted that invasive disease such as meningitis, bacteraemia and bacteraemic pneumonia significantly impact patients, their family/whānau and society. The Committee considered that pneumococcal infection can also result in non-invasive disease (eg non-bacteraemic pneumonia and acute otitis media) that creates an additional burden and high health need. The Committee noted the health need in paediatric populations and in adults with underlying conditions is reflected in the currently funded groups for PCV13 and PPV23.

5.9. The Committee considered it important for pneumococcal vaccine funding and immunisation schedule decisions to be informed by serotype surveillance and the burden of IPD and non-invasive pneumococcal disease. The Committee considered that achieving herd immunity against pneumococcal disease is reliant on vaccination of the eligible infant population and that any improvement in herd immunity with a new, higher valent pneumococcal vaccine such as PCV15 would likely be small and gradual when compared with vaccination with PCV13, but should show benefits relatively quickly compared with PCV10.

5.10. The Committee noted year-to-date (to July 2022) cumulative totals for IPD serotypes by year as provided by the Public Health Agency, which showed serotype 19A was the most commonly reported vaccine (PCV13) preventable serotype for 2020-2022. The Committee also noted serotype data from the Institute of Environmental Science and Research (ESR) on rising 19A levels and considered these rates were at a record high level.

5.11. The Committee considered that the additional two serotypes included in PCV15 (22F and 33F) are considered serotype replacers and there is a risk they could become more prevalent once 19A is better controlled. The Committee noted that 22F was the third most common IPD isolate in New Zealand in 2017-19, that 22F and 33F are associated with a risk of antimicrobial resistance, and that both serotypes are covered by the PPV23 vaccine.

5.12. The Committee considered that Māori are disproportionately affected by IPD in terms of incidence and mortality, and noted that the risk of IPD for Māori is over three times higher than the risk for New Zealand Europeans (Immunisation Advisory Centre, 2020). The Committee noted that the Immunisation Subcommittee previously considered that Māori were over-represented in the serotype 19A cases that occurred in 2020 in children under five years of age. The Committee considered that it was not known, based on current data, whether a disproportionate number of cases of adults with serotypes 22F or 33F were Māori.

5.13. The Committee noted that the risk of developing IPD for Pacific peoples was almost four times the risk for New Zealand Europeans (Immunisation Advisory Centre, 2020) and that of eight deaths in children under five years of age in 2020-21, three were cases of serotype 19A disease and all were Pacific children.

5.14. The Committee noted that higher rates of IPD are also seen in more socio-economically deprived populations and considered that while increased protection from vaccination has the potential to improve inequities, the additional serotype coverage in PCV15 would be unlikely to improve inequities to a greater extent than PCV13.

Health Benefits

5.15. The Committee noted that PCV15 (Vaxneuvance) is a 15-valent pneumococcal conjugate vaccine which includes serotype-specific capsular polysaccharides included in PCV13, plus two additional serotypes; 22F and 33F, each conjugated to a non-toxic fragment of the diphtheria toxin (CRM197 protein). The Committee noted that the application proposes PCV15 replace both PCV10 and PCV13 in their current funded populations (ie 2+1 dosing schedule for children under 5 years of age, a 3+1 dosing schedule for children at higher risk, and up to four additional doses for the currently funded high risk groups). The Committee noted that an application for PCV15 approval had been submitted to Medsafe in April 2022.

5.16. The Committee noted the unpublished evidence from the Clinical Study Reports (CSRs) of the following phase III, multicentre, randomised, double-blind clinical trials that investigated PCV15 compared with PCV13 in paediatric patient populations according to either 2+1 or 3+1 dose schedules:

- PNEU-STEM P022
- PNEU-SICKLE P023
- PNEUPLAN P024
- PNEU-PED-EU-1 P025
- PNEU-PED-EU-2 P026
- PNEU-DIRECTION P027
- PNEU-PED P029
- PNEU-WAY PED P030
- PNEULINK P031

5.17. The Committee noted the following evidence from phase III, multicentre, randomised, double-blind clinical trials, most of which investigated PCV15 compared with PCV13 in adult populations:

- Hammit et al. Open Forum Infect Dis.2021;9:ofab605
- Mohapi et al. AIDS. 2022;36:373-82
- Song et al. Vaccine. 2021;39:6422-36
- Platt et al. Vaccine. 2022;40:162-72
- Simon et al. Vaccine. 2022;40:1342-51
- Severance et al. Hum Vaccin Immunother. 2022;18:1-14 (investigating PCV15 and concomitant quadrivalent influenza vaccine)

5.18. The Committee was made aware of a summary of evidence from most of the above trials that was presented by the US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) in June 2022, which pooled data due to small numbers and highlighted that:

5.18.1. The P008, P024, P027 and P029 immunogenicity/efficacy studies did not report correlates of protection for some critical outcomes in healthy infants

5.18.2. The P030 study in HIV positive individuals ages 6-17 years reported higher immune response with PCV15 and PPV23 vs PCV13 and PPV23 for three of 13 PCV13 serotypes, but not for the unique serotypes 22F and 33F

5.18.3. The potential risk of increased harm or benefit cannot be excluded from the P008, P029, P027, P024, and P031 studies in children less than two years of age due to imprecision from few reported vaccine-related side effects and wide confidence intervals for relative risk

5.18.4. Safety risk in those aged two to 18 years with underlying conditions (HIV or sickle cell anaemia) was not estimable due to small sample size in the P023 and P030 studies and no serious vaccine-related side effects being reported.

5.18.5. The Committee was also made aware of the ACIP recommendation for PCV15 followed by PPV23 (or a single dose of PCV20, where funded) in adults 65 years of age and older and for those with chronic medical conditions or immunocompromise (aligned with current recommendation for PCV13 followed by PPV23).

5.19. The Committee noted that most serotypes had lower titres following PCV15 compared with PCV13, however, noted that the trials were designed to demonstrate

non-inferiority. The Committee considered that the immunogenicity outcomes [specifically, the statistically significant geometric mean titres (GMTs) and geometric mean concentrations (GMTs)] for serotype 19A in the P025 and P026 paediatric trials likely reflected adequate coverage relative to that of PCV13. The Committee noted differences in 22F and 33F outcomes between PCV13 and PCV15 due to the additional cover with PCV15.

5.20. The Committee considered that most of the clinical trials provided included small patient numbers and noted that the strength and quality of evidence for PCV15 compared with PCV13 was quite poor, given it was based on immunogenicity data without clinical effectiveness data, although considered this was not uncommon for vaccine research.

5.21. The Committee noted the following conference presentation slides and poster presenting epidemiological data arising from changes in PCV vaccine types in Belgium and considered that similar benefits (ie a reduction in serotype 19A carriage) could be expected in New Zealand from a change to PCV15 or PCV13 from PCV10:

- The evolution of PCV13-non-PCV10 serotypes in adults during the use of different PCVs in the Belgian childhood vaccination programme (Cuypers et al. 2022).
- A reduction in serotype 19A IPD in youngest children in the second year post re-switch from PCV10 to PCV13 in Belgium (Cuypers et al. 2022).
- Carriage of serotype 19A decreased substantially in Belgian children attending daycare centres two years after the PCV10 to PCV13 switch (Ekinci et al. 2022).

5.22. Overall, the Committee noted that the evidence indicated the non-inferiority of PCV15 to PCV13. The Committee considered that this was sufficient to consider the two comparable in terms of benefit at a population level and therefore PCV15 would be considered interchangeable with PCV13. The Committee considered that a 2+1 infant dosing schedule would be appropriate with PCV15 for healthy full-term infants, however, considered that it would be reasonable to continue use of a 3+1 dosing schedule for high-risk children and up to four additional doses for the currently funded high-risk groups in the absence of evidence for efficacy outcomes with PCV15 in high-risk people.

5.23. The Committee considered that, based on this appraisal and noting previous advice regarding the comparability of PCV10 and PCV13, PCV15 would be non-inferior to both PCV10 and PCV13 in the currently funded population groups and therefore could replace either PCV10 or PCV13 in the Childhood Immunisation Schedule. The Committee considered that it would like to review pneumococcal vaccines for use in adults at a future meeting.

Suitability

5.24. The Committee considered that with any change in pneumococcal vaccine strategy it remains essential that serotype surveillance and monitoring of invasive and non-invasive pneumococcal disease epidemiology be continued, with established IPD thresholds for timely and reactive action.

5.25. The Committee considered that PCV15 would be suitable as a single funded pneumococcal conjugate vaccine for prevention of pneumococcal disease in the proposed populations including high-risk groups, noting that PPV23 would still be required in addition for high-risk groups. The Committee considered that people who

received at least one PCV10 dose would require a catch-up dose, but it would be reasonable for those who received at least one PCV13 dose to complete their course with PCV15 without a catch-up programme. The Committee considered that PCV15 would be suitable for use in testing for primary immunodeficiency diseases.

5.26. The Committee considered that the presentation of PCV15 appeared similar to that of PCV13 and therefore no administration issues or suitability concerns were expected.

Costs and Savings

5.27. Members considered that assessment of potential costs and savings with PCV15 could take into account costs arising from IPD and from non-invasive disease (eg pneumonia, otitis media) based on a potentially likely benefit with PCV15 vs PCV13. However, the Committee considered the magnitude of these outcomes was uncertain and would depend on the possible emergence of serotypes 22F and 33 F in future.

Summary for Assessment

5.28. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for PCV15 if it were to replace either PCV10 or PCV13 in the Pharmaceutical Schedule with a 2+1 dosing schedule for children under 5 years of age, a 3+1 dosing schedule for children at higher risk, and up to four additional doses for the currently funded high-risk groups. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Populations covered in the restriction criteria for the PCV10 and PCV13 vaccines
Intervention	Same dosing as for PCV10 and PCV13, ie: • 2+1 dosing for infants up to the age of 59 months • 3+1 dosing schedule for children at higher risk, • Two doses for high-risk children under 5 years and up to three doses for infants under 1 year who have previously received any doses of PCV10 • Up to 4 additional doses for high-risk children aged under 5 years with specified medical conditions listed in the Pharmaceutical Schedule for PCV13 • Up to 4 additional doses for high-risk people aged over 5 years with specified medical conditions listed in the Pharmaceutical Schedule for PCV13 For use in testing for primary immunodeficiency diseases
Comparator(s)	PCV10 and PCV13
Outcome(s)	Equivalent efficacy and safety vs currently funded PCV10 and PCV13 vaccines
Table definitions: **P**opulation: the target population for the pharmaceutical; **I**ntervention: details of the intervention pharmaceutical; **C**omparator: details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); **O**utcomes: details the key therapeutic outcome(s) and source of outcome data.	

6. High dose quadrivalent influenza vaccine for people aged 65 years and over and for Māori and Pacific people aged 60 years and over

Application

6.1. The Advisory Committee reviewed a supplier application for the listing of Fluzone high dose quadrivalent influenza vaccine (HD-QIV) in the Pharmaceutical Schedule as the seasonal influenza vaccination for people aged 65 years and over, and for Māori and Pacific people aged 60 years and over

6.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

6.3. The Advisory Committee **recommended** that the high dose quadrivalent influenza vaccination be listed with a **high priority** for people aged 65 years and older within the context of vaccines and immunisation.

6.4. The Advisory Committee **recommended that** the high dose quadrivalent influenza vaccination be listed with a **high priority** for Māori and Pacific people aged 60 years and over, within the context of vaccines and immunisation.

6.5. In making this recommendation the Committee considered the high health need of the elderly population with regard to influenza and associated complications, the limited efficacy of currently available vaccinations for this population, inequitable health outcomes relating to influenza in the Māori and Pacific population, and the evidence of benefit with HD-QIV.

6.6. The Committee noted its previous cost neutral recommendation for adjuvanted quadrivalent influenza vaccination (Fluad Quad). The Committee considered that although its recommendations for Fluad Quad and Fluzone high dose are different, it has no preference between the two vaccines as there are no head-to-head comparisons or evidence that one is more effective than the other. The Committee considered that either vaccine would be more effective for the population aged 65 years and over than the currently funded QIV. The Committee considered that both high dose quadrivalent influenza vaccine and adjuvanted quadrivalent influenza vaccine should be included in the next commercial process for influenza vaccines, and that there is no quantitative difference between the two vaccines at present.

Discussion

Māori Impact Statement

6.7. The Committee discussed the impact of funding Fluzone high dose QIV on Māori health areas of focus and Māori health outcomes. The Committee noted that Māori people are at a higher risk of complications from influenza, and at a younger age than non-Māori.

Health Need

6.8. The Committee noted that influenza and its impacts on patients and their family and whānau have been previously well described. The Committee noted that the risk of influenza and influenza-related complications is higher for Māori and Pacific people. The Committee noted that Māori and Pacific peoples are more likely to be hospitalised from severe acute respiratory infections (SARI; 243.2 and 307.2 per 100,000 respectively) compared with non-Māori and non-Pacific populations (111.9 per 100,000 for 'Other' and 53.0 for Asian people) and are also more likely to have

to be treated in ICU due to SARI, though Māori rates of ICU admission from confirmed influenza are lower than for non-Māori (ESR 2019 Influenza Surveillance intelligence dashboard).

6.9. The Committee noted that estimated influenza hospitalisation rates were 58.1 per 100,000 for the European population compared with 80.0 and 83.0 per 100,000 for Māori and Pacific people, respectively (Khieu et al. Vaccine 2015;33:4087-92). The Committee also noted a 2017 publication which reported that when standardising for age, the mortality rate attributable to influenza in the Māori population was statistically significantly higher than Other/European populations with 21.1 per 100,000 compared with 4.5 per 100,000 for European/Other. The Pacific population also experienced a statistically significantly higher rate of influenza attributable mortality compared with European/Other with a rate of 6.8 per 100,000 (Khieu et al. J Infect. 2017;75:225-33).

6.10. The Committee noted that the funded influenza vaccine for the 2022 influenza season in New Zealand was a standard dose QIV (Afluria Quad). The Committee noted that for the 2022 season the vaccine offers protection against strains A/Victoria/2570/2019 (H1N1) pdm09-like virus, A/Darwin/9/2021 (H3N2)-like virus, B/Austria/1359417/2021-like virus, B/Phuket/3073/2013-like virus.

6.11. The Committee noted that, elderly people, especially those with comorbidities and frailty, also are at high risk of influenza-related complications and noted that traditional trivalent (TIV) and quadrivalent (QIV) influenza vaccines have limited efficacy in this population. The Committee noted that influenza vaccination claims data for 2021 show that the total overall coverage rate for adults aged 65 years and over was 63.8%, 50% for Māori aged 65 years and over, and 62.4% for Pacific people aged 65 years and over

Health Benefit

6.12. The Committee noted that the high dose quadrivalent influenza (HD-QIV) Fluzone vaccine is an inactivated virus vaccine which provides active immunisation against each of four influenza virus strains (A/H1N1, A/H3N2, and one B strain from each of the Victoria and Yamagata lineages) via humoral antibodies against the haemagglutinins for each strain. The Committee noted that Fluzone contains 240 micrograms (µg) influenza virus haemagglutinin (HA) per 0.7 mL dose (pre-filled) in the recommended ratio of 60 µg HA of each of the four strains recommended for the given influenza season.

6.13. The Committee noted that funding was requested for those aged 65 years and over, and 60 years and over for Māori and Pacific people. The Committee noted that Fluzone high-dose QIV was not yet approved by Medsafe.

6.14. The Committee noted the following evidence relating to the use of high dose QIV (HD-QIV):

6.14.1. Falsey et al. J Infect Dis. 2009;200:172-80 (FIM05): a multicentre randomised, double-blind, controlled phase III non-inferiority trial of standard dose trivalent influenza vaccine (SD-TIV) versus HD-QIV in subjects aged 65 years or older who were medically stable (2006 influenza season). Geometric mean titre (GMT) rises with the HD-QIV were 1.3-1.7 times higher than with HD-TIV. A significantly higher percentage of subjects in the HD group had postvaccination hemagglutination inhibition titres for A/H1N1, A/H3N2, and B of at least 1:80 (73% vs. 51%; 97% vs. 89%; 52% vs. 485; all P values <0.001) and 1:160 (45%

vs. 26%; 91% vs. 78%; 22% vs. 16%; all P values <0.001), compared to subjects in the SD vaccine group. The HD vaccine was inferior to the SD vaccine with respect to moderate to severe fever, with a relative risk of 3.6 (95% CI 1.25–10.08).

6.14.2. DiazGranados et al. N Engl J Med. 2014;371:635-45 (FIM12): a phase IIIb/IV multicentre, randomised, double-blind, active-controlled trial of SD-TIV versus HD-TIV in adults aged 65 years or older (2011-2013 influenza seasons). The efficacy of HD relative to SD for the primary end point (the occurrence, at least 14 days after vaccination, of laboratory-confirmed influenza) was 24.2%. The relative vaccine effectiveness statistically significantly favoured HD-TIV for the prevention of serious cardio-respiratory events and pneumonia events. Subjects who received the HD-TIV had higher rates of injection site reactions, myalgia, shivering and headache.

6.14.3. DiazGranados et al. Vaccine. 2015;33:4988-93 (FIM12): investigated the effectiveness of HD-TIV compared to SD-TIV in preventing serious illnesses considered potential sequelae or complications of influenza infection from the FIM12 study. Rates of all-cause hospitalisation did not differ between groups in Year 1, whereas they were significantly lower for the HD group in Year 2; for both study years combined, the rate of all-cause hospitalization was 6.9% (95% CI, 0.5–12.8%) lower in the HD group. The relative vaccine effectiveness of HD relative to SD for all-cause hospitalisation, serious cardio-respiratory events and pneumonia events statistically significantly favoured HD-TIV. Three serious adverse events were considered to be related to the high dose vaccine; cranial nerve VI palsy, hypovolemic shock secondary to diarrhoea, and acute disseminated encephalomyelitis. No serious adverse events for the standard dose group were considered to be related to the vaccine.

6.14.4. Chang et al. Vaccine. 2019;37:5825-34: a randomised, modified double-blind, active-controlled, multicentre trial of HD-QIV or HD-TIV (two vaccines with differing B-strains) in adults aged 65 years or over. For all four strains, HAI GMTs and seroconversion rates induced by HD-QIV were reported to be non-inferior to those induced by HD-TIVs containing the same strains. For both B strains, HAI GMTs and seroconversion rates induced by HD-QIV were superior to those induced by HD-TIV not containing the same B-strain lineage. For the two B-lineage strains, post-vaccination seroneutralisation GMTs and geometric mean post-/pre-vaccination titre ratios (GMTRs) were similar for IIV4-HD and HD-TIV when it contained the same B-lineage strain but higher for HD-QIV when it contained the B-lineage strain not included in the HD-TIV. Proportions reporting all injection-site reactions, as well as myalgia, shivering, and headache were higher for HD-QIV than for HD-TIV.

6.14.5. Pepin et al. Hum Vaccin Immunother. 2021;17:5475-86: a randomised phase III modified double-blind, active-controlled study of HD-QIV versus SD-QIV in people aged 60 years and over. At day 28, GMTs for the four influenza strains had increased compared with baseline and were higher in the HD group than the SD group. GMTs in the HD group were higher in the 60–64 age-group than the ≥65 age-group for the A/H1N1, B/Maryland, B/Phuket strains and were similar between age-groups for the A/H3N2 strain. Seroconversion rates were also reported to be higher for the HD group compared with the SD group for the four influenza strains. Injection site pain was more common in the HD group in both 60-64 and 65+ age groups. The most common Grade 3 adverse reaction was erythema, reported by eight (2.1%) participants in the HD group and one (0.3%) participant in the SD group.

6.14.6. Lee et al. Expert Rev Vaccines. 2018;17:435-43: a systematic review and meta-analysis of trivalent high dose versus standard dose influenza vaccine reported a moderate but non-statistically significant impact against death following admission or emergency department visit for influenza (relative vaccine effectiveness [rVE] = 22.2%; 95% CI: −18.2 to 48.8; p = 0.240). Limited benefit was observed against all-cause mortality (rVE = 2.5%; 95% CI: −5.2 to 9.5; p = 0.514). rVE for hospital admissions from flu was reported as 17.8% (95% CI 8.1 to 26.5).

6.14.7. Woo et al. Vaccine. 2022;40:1026-30: A review and summary of reports of adverse events after QIV-HD to the Vaccine Adverse Event Reporting System (VAERS). From July 30, 2020, through June 30, 2021, VAERS received 2,122 reports after QIV-HD. The vast majority (2,018; 95.1%) were non-serious and included events that had been observed in the prelicensure clinical trial, such as injection site reactions, fever, headache, and nausea. The most common serious events included Guillain-Barré syndrome, cellulitis or other local reactions, constitutional signs/symptoms (eg fever), and cardiovascular events.

6.14.8. Izikson et al. Lancet Respir Med. 2022;10:392-402: an ongoing phase II open-label descriptive trial aiming to assess the safety and immunogenicity of concomitant administration of high-dose quadrivalent influenza vaccine (QIV-HD) and a mRNA-1273 (Moderna) COVID-19 vaccine booster dose in adults aged 65 years and over. Reactogenicity profiles were similar between the coadministration and mRNA-1273 (COVID19 vaccine) groups, with lower reactogenicity rates in the QIV-HD group (frequency of solicited injection site reactions 86·0% [95% CI 77·6–92·1], 91·3% [84·2–96·0], and 61·8% [50·9–71·9]; frequency of solicited systemic reactions 80·0%, [70·8–87·3], 83·7% [75·1–90·2], and 49·4% [38·7–60·2], respectively). There were no serious adverse events, adverse events of special interest, or deaths.

6.15. The Committee noted that the Australian Technical Advisory Group on Immunisation (ATAGI) states in their 2022 guidance document that there is no preference for use between either Fluad Quad or Fluzone High Dose Quadrivalent in the 65+ age group, and that either is preferred over a standard dose vaccine for this age group. The Committee noted that there are no head-to-head trials between these two vaccines.

6.16. The Committee noted that standard dose influenza vaccines also provide limited efficacy for individuals who are severely immunocompromised and noted that there is some limited evidence relating to the use of high dose influenza vaccines in this population.

6.17. The Committee considered that uptake of influenza vaccination would potentially increase if the vaccine were able to be administered concomitantly with COVID-19 vaccinations.

Suitability

6.18. The Committee noted that Fluzone HD-QIV is to be stored at 2-8 degrees and that the shelf life of Fluzone HD-QIV is 12 months. The Committee considered that this is an appropriate shelf-life for a single influenza season. The Committee noted that having a vaccine for the elderly population which is different from the general population means that vaccination providers will have to store multiple brands, doses, and types of vaccine in their fridges. The Committee considered that this creates a small risk of incorrect vaccines being administered (for example, the high

dose vaccine being administered to children), but noted that providers already mitigate these risks.

6.19. The Committee considered that the increased reactogenicity of the high dose vaccine compared to standard dose would need to be monitored but did not consider that this would impact uptake.

Summary for Assessment

6.20. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for Fluzone high dose quadrivalent influenza vaccine if it were to be funded in New Zealand for people aged 65 years and over, and Māori and Pacific people aged 60 years and over. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People aged 65 years and over. Māori and Pacific people aged 60 years and over.
Intervention	High dose influenza vaccination
Comparator(s)	Standard dose influenza vaccination
Outcome(s)	*Outcomes with high certainty* Reduced influenza infections Reduced outpatient visits Reduced inpatient events *Outcomes with low certainty* Reduced mortality
Table definitions: **P**opulation: the target population for the pharmaceutical; **I**ntervention: details of the intervention pharmaceutical; **C**omparator: details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); **O**utcomes, details the key therapeutic outcome(s) and source of outcome data.	

7. Quadrivalent influenza virus haemagglutinin, surface antigen, inactivated, prepared in cell cultures

Application

7.1. The Advisory Committee reviewed the supplier application for Flucelvax® Quad (QIVc), a surface antigen, inactivated quadrivalent influenza vaccine manufactured using cell-based technology (as opposed to grown in eggs).

7.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

7.3. The Advisory Committee **recommended** that quadrivalent influenza virus haemagglutinin, surface antigen, inactivated vaccine prepared in cell cultures be

listed with a **medium** priority for persons aged ≥6 months to <65 years who have certain medical conditions that increase the risk of influenza disease complications, within the context of vaccines and immunisation, subject to the following eligibility criteria:

INFLUENZA VACCINE
Is available for:

a) people under 65 years of age who:
    a. have any of the following cardiovascular diseases:
        i. ischaemic heart disease, or
        ii. congestive heart failure, or
        iii. rheumatic heart disease, or
        iv. congenital heart disease, or
        v. cerebrovascular disease; or
    b. have either of the following chronic respiratory diseases:
        i. asthma, if on a regular preventative therapy, or
        ii. other chronic respiratory disease with impaired lung function; or
    c. have diabetes; or
    d. have chronic renal disease; or
    e. have any cancer, excluding basal and squamous skin cancers if not invasive; or
    f. have any of the following other conditions:
        i. autoimmune disease, or
        ii. immune suppression or immune deficiency, or
        iii. HIV, or
        iv. transplant recipients, or
        v. neuromuscular and CNS diseases/disorders, or
        vi. haemoglobinopathies, or
        vii. are children on long term aspirin, or
        viii. have a cochlear implant, or
        ix. errors of metabolism at risk of major metabolic decompensation, or
        x. pre and post splenectomy, or
        xi. Down syndrome, or
    g. are pregnant; or

b) people under 65 years of age who:
    a. have any of the following serious mental health conditions:
        i. schizophrenia, or
        ii. major depressive disorder, or
        iii. bipolar disorder, or
        iv. schizoaffective disorder, or
        v. are currently accessing secondary or tertiary mental health and addiction services

7.4. The Advisory Committee **recommended** that quadrivalent influenza virus haemagglutinin, surface antigen, inactivated vaccine prepared in cell cultures be listed with a **medium** priority for Māori and Pacific people aged ≥55 to <65 years, within the context of vaccines and immunisation, subject to the following eligibility criteria:

INFLUENZA VACCINE
Is available for:

a) people 55 to 64 years of age (inclusive) and are Māori or any Pacific ethnicity

7.5. The Advisory Committee **recommended** that quadrivalent influenza virus haemagglutinin, surface antigen, inactivated vaccine prepared in cell cultures be listed as **cost neutral** to the currently funded Afluria Quad vaccine, within the context of vaccines and immunisation, subject to the following eligibility criteria:

INFLUENZA VACCINE
Is available for:

a) all people 65 years of age and over

7.6. The Advisory Committee **recommended** that quadrivalent influenza virus haemagglutinin, surface antigen, inactivated vaccine prepared in cell cultures be listed with a **high** priority for persons aged ≥6 months to <3 years who have certain medical conditions that increase the risk of influenza disease complications, within the context of vaccines and immunisation.

7.7. In making these recommendations, the Advisory Committee noted the evidence of non-inferiority of QIVc compared to QIVe, the reduced impact of QIVc on the environment, and the supply chain improvements with QIVc.

Discussion

Māori Impact Statement

7.8. The Committee noted in earlier discussions on influenza and vaccination at this meeting, that influenza (and its complications) disproportionately affects Māori and at a younger age, compared to non-Māori. The Committee noted that, according to Khieu et al. (J Infect. 2017;75:225-33), the estimated average annual number and rate (per 100,000 people) of influenza-attributable deaths (by ethnicity and age group) for Māori aged <64 years is 5.4 compared with 2.0 for those of European descent.

Health Need

7.9. The Committee noted that influenza and its impacts on patients and their family and whānau have been previously well described, most recently at the May 2022 Immunisation Advisory Committee meeting, and in the discussion for Fluzone High Dose influenza vaccine also discussed at this meeting. The Committee noted that influenza and related complications in New Zealand disproportionately affect Māori and Pacific populations.

7.10. The Committee noted that a recent study on respiratory mortality and hospitalisations associated with influenza in Australia reported that people aged 0-6 years and 65 years or more had the highest rates of influenza related hospitalisations (165.16 and 206.57 per 100,000, respectively) and deaths (3.74 and 31.71 per 100,000, respectively; Leung et al. Int J Epidemiol. 2022;51:458-67), and noted that this trend is also seen in New Zealand.

7.11. The Committee noted that the currently funded adult annual influenza vaccine is Afluria Quad, an egg-based quadrivalent inactivated influenza vaccine (QIVe) suspension for injection which is funded for everyone aged 65 years or over, for people aged 55 to 65 who are Māori or Pacific (for the 2022 season only), and for people between the ages of three and 64 who have underlying conditions such as cardiovascular disease, respiratory disease, or other chronic illness. The Committee noted New Zealand surveillance data for influenza does not provide specific information on influenza incidence or outcomes for these groups. The Committee also noted that Afluria Quad Jr contains the same strains of Afluria Quad, but at a lower dose and is funded for children aged 6 to 35 months if they have underlying conditions.

7.12. The Committee noted that the influenza virus can change rapidly between, and within, influenza seasons. This can lead to new strains circulating in a seasonal pattern, and that antigenic mismatch between the seasonal vaccine strains and the

circulating viruses can negatively affect influenza vaccine efficacy and effectiveness. The Committee noted that egg-adaptation (mutations that occur in the receptor binding region of haemagglutinin allowing influenza viruses to infect avian cells more efficiently when grown in eggs) can include changes to key viral antigens resulting in antigenic mismatch to circulating viruses and thereby reduced vaccine effectiveness (Wu et al. PLoS Pathog. 2017;13:e1006682). The Committee also noted that antigenic changes in egg-based vaccines contribute to new influenza-A subtypes, which are associated with pandemics, and that egg-adaptation remains a concern for the H3N2 virus, a highly virulent influenza sub-type in terms of morbidity and mortality (Joint Committee on Vaccination and Immunisation (JCVI): Advice on influenza vaccines for 2022/23).

Health Benefit

7.13. The Committee noted that Flucelvax Quad (QIVc) is a surface antigen, inactivated quadrivalent influenza vaccine that is manufactured using cell-based technology (as opposed to grown in eggs). The Committee noted that the cell-based technology is designed to eliminate egg-adaptation of the virus strains used in vaccine manufacture.

7.14. The Committee noted that the JCVI advice on influenza vaccines for the 2022/23 influenza season is that at-risk adults (including pregnant women) aged less than 65 years and children aged two to less than 18 years of age in an at-risk group who cannot receive live attenuated influenza vaccine should receive QIVc. The Committee also noted that Flucelvax Quad is Medsafe approved for the prevention of influenza caused by Influenza Virus Types A and B contained in the vaccine, and that vaccine is approved for use in adults and children nine years of age and older. The Committee noted that the supplier had indicated that an application to extend the indications for Flucelvax Quad to people aged ≥6 months was recently submitted to Medsafe and is under initial evaluation.

7.15. The Committee noted a retrospective assessment of the antigenic similarity of egg-propagated and cell culture-propagated reference influenza virus strains as compared with the circulating virus strains across the 2002-2003 and 2017-2017 influenza seasons (Rajaram et al. Int J Environ Res Public Health. 2020;17:5423). The Committee noted that the egg-propagated reference viruses were well matched against circulating viruses for A/H1N1 and B/Yamagata, whilst A/H3N2 and B/Victoria cell-propagated reference viruses appeared to be more antigenically similar to circulating A/H3N2 and B/Victoria viruses.

7.16. The Committee noted the following publications which provided additional evidence regarding the immunogenicity and vaccine effectiveness of QIVc:

- Dawood et al. Clin Infect Dis. 2021;73:1973-81
- Moehling et al. Vaccine. 2020;38:5171-77
- Bruxvoort et al. Vaccine. 2019;37:5807-11
- DeMarcus et al. Vaccine. 2019;37:4015-21
- Boikos et al. Clin Infect Dis. 2020;71:e665-e671
- Divino et al. Vaccine. 2020;38:6334-43
- Klein et al. PLoS One. 2020;15:e0229279
- Martin et al. J Infect Dis. 2021;223:2062-71
- Boikos et al. Clin Infect Dis. 2021;73:e692-e698
- Boikos et al. Open Forum Infect Dis. 2021;8:ofab167

- Krishnarajah et al. Vaccines (Basel).2021;9:80
- Divino et al. Open Forum Infect Dis. 2021;9:ofab604

7.17. The Committee noted that relative vaccine effectiveness favoured QIVc over QIVe for the ≥4 and 4-64 age groups against any influenza strain in six retrospective cohort studies. The Committee noted that the vaccine is not designed to address immunosenescence and therefore funding for adults aged ≥ 65 years is not requested.

7.18. The Committee considered the strength and quality of evidence to be low. The Committee considered that QIVc was non-inferior to QIVe. The Committee considered it unlikely that randomised control trials comparing QIVc with QIVe would be conducted for influenza.

7.19. The Committee noted that the available evidence does not indicate superior vaccine effectiveness of QIVc over QIVe and considered that the main advantages of using cell-based technologies to be the elimination of antigenic changes during vaccine manufacture.

Suitability

7.20. The Committee also noted the negative environmental impact associated with egg-based vaccine manufacture. The Committee considered that using a cell-culture propagated vaccine would allow production of QIVc to increase rapidly in response to high demand or a pandemic, and that reducing the reliance on chickens and eggs reduces supply chain risk. The Committee also noted the significantly lowered environmental supplier impact with QIVc compared to QIVe by no longer having to dispose of large quantities of embryonated chicken eggs daily. The Committee also noted the reduced need for antibiotic usage for animal welfare during manufacturing.

7.21. The Committee noted that the dosage of Flucelvax is the same for adults and children and considered that this would be beneficial for those administering vaccinations as the risk of giving the incorrect dose would be reduced.

Costs and Savings

7.22. The Committee considered that data on influenza-like-illness (ILI) in New Zealand is reliable, and that any influenza related economic modelling by Pharmac staff should focus on available severe acute respiratory infections (SARI) and hospitalisation data. The Committee considered that Australian ILI data collection is robust and considered that ILI surveillance in Australia may better capture ILI burden compared to New Zealand ILI surveillance. The Committee considered ILI surveillance data in Australia could be generalisable to New Zealand but noted there are some limitations as circulating strains are sometimes different between the two countries. The Committee considered where available, New Zealand influenza data is best to use for modelling purposes and Australian data could be considered in sensitivity analysis.

Summary for Assessment

7.23. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for Flucelvax Quad if it were to be funded in New Zealand. This PICO captures key clinical aspects of the proposal and may be used to frame

any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	• People aged ≥6 months to <65 years who have certain medical conditions that increase the risk of influenza disease complications (includes pregnant women and people with serious mental health conditions).	• Māori and Pacific people aged ≥55 to <65 years	• People aged ≥6 months to <3 years	• People aged 65 years and over
Intervention	Annual dose of QIV cell-based vaccine (Flucelvax Quad)			
Comparator(s)	Annual dose of QIV egg-based vaccine (Afluria Quad/Afluria Quad Jr)			
Outcome(s)	• Reduced outpatient influenza cases • Reduced hospitalised influenza cases			
Table definitions: **P**opulation: the target population for the pharmaceutical; **I**ntervention: details of the intervention pharmaceutical; **C**omparator: details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); **O**utcomes: details the key therapeutic outcome(s) and source of outcome data.				

8. DTPa-hepB-IPV-Hib - Vaccination of infants from six weeks of age against DTPa-hepB-IPV-Hib

Application

8.1. The Committee noted that Pharmac sought updated advice from the Committee regarding the diphtheria, haemophilus influenzae type B, pertussis, tetanus, polio, hepatitis B (DTPa-hepB-IPV-Hib) vaccine (Hexaxim), in light of a clinical data update provided by the supplier in July 2022 from clinical trials and relevant studies that have been conducted since it was last considered in 2015.

8.2. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

8.3. The Committee **recommended** that consideration of the appropriateness of any change to DTPa-hepB-IPV-Hib (Hexaxim) through any vaccines commercial process be **deferred** until data regarding [redacted] real world observational data on the

reactogenicity and immunogenicity of concomitant administration with meningococcal B vaccine (Bexsero).

8.4. The Committee noted that there is not currently a pertussis-containing dose in the second year of life, and considered that it would like to review the need for an additional dose at a future meeting.

Discussion

Māori Impact Statement

8.5. The Committee noted there is overall low vaccination coverage for Māori infants compared with non-Māori infants and noted that pertussis disease conveys a significant burden for Māori. The Committee considered there were unacceptable inequities in this space.

Background

8.6. The Committee noted the initial proposal received from Sanofi-Pasteur in response to Pharmac's June 2013 Immunisation Request for Proposals was for consideration of Hexaxim (DT2aP-HBV-IPV-Hib), as a possible replacement for Infanrix Hexa (DT3aP-HBV-IPV/Hib) immunisation at six weeks, three months and five months of age.

8.7. The Committee noted that in November 2013, PTAC reviewed a Pharmac paper seeking advice on the suitability of Hexaxim and recommended that Pharmac not change to a vaccine containing a two-component acellular pertussis (2aP) at that time, and it also did not recommend changing when infant vaccination rates were less than 95%.

8.8. The Committee (formerly known as the Immunisation Subcommittee) noted that it considered Hexaxim in October 2015 following its Medsafe approval in 2014. At that time, the Subcommittee recommended that Hexaxim was a suitable product for the schedule and recommended seeking international advice regarding whether any change from a 15-month Hib vaccine to a hexavalent vaccine would be appropriate. The Subcommittee recommended not changing to a 2+1 dosing regimen and to a two-component vaccine at the same time, noting that very close monitoring would be required if either change were to occur. The Committee noted that the Subcommittee had raised a question around hepatitis B vaccination based on review in Australia, however, the Committee considered that there was an error in the previous minutes and that this should have referred to an extra dose of the pertussis vaccine in the second year of life (ie ~~Hep B~~ DTaP booster).

Health Need

8.9. The Committee noted that previous advice has described the health need arising from pertussis (whooping cough), the inequity and increased for burden for very young infants (especially those less than six months of age), and the significant burden for Māori and Pacific peoples. The Committee reiterated the benefits of avoiding pertussis disease for patients, whānau, and society.

8.10. The Committee noted that there is overall low vaccination coverage for Māori infants compared with non-Māori infants at six months of age, a timepoint used as a marker for timely receipt of infant vaccines including pertussis. The Committee noted that these rates have fallen in New Zealand from a high of around 80% in early 2020 to 67.2% for all infants at June 2022, and to 45.9% for Māori infants (Ministry of Health.

2022). The Committee considered that this data reflected unacceptable inequities in this space.

8.11. The Committee considered that the overall rates of vaccinations completed on time were also decreasing. However, members considered that immunisation rates against pertussis in pregnancy have been improving, since Boostrix was funded for pregnant women outside pertussis epidemics in 2015. Members noted that a lot of effort has gone into promotion of pertussis immunisation in pregnancy, including through the New Zealand College of Midwives.

8.12. The Committee was made aware of data extracted from the WHO Immunisation Data portal in September 2022, reporting low incidence of pertussis infection in Sweden and in Belgium, each with over 97% vaccine coverage using two component (2aP) and/or three component (3aP) acellular pertussis vaccines and either 2+1 (Sweden) or 3+1 (Belgium) dosing schedules. The Committee considered this was not comparable to New Zealand given the differences in pertussis epidemiology.

8.13. The Committee considered that New Zealand is due for another pertussis epidemic based on previous three- to five-year cycles. The Committee was made aware of evidence that vaccine-evasive or resistant strains (especially pertactin deficient strains) are emerging, are increasingly circulating due to use of acellular pertussis (aP), and that those vaccinated with aP are more susceptible to pertactin deficient strains (Barkoff et al. Euro Surveill. 2019;24:1700832; Jayasundara et al. Epidemics. 2020;31:100388). However, the Committee considered that the impact of 2aP vs 3aP vaccines on this was unclear and it was not aware of the prevalence of these strains in New Zealand.

8.14. The Committee noted that noted DT3aP-HBV-IPV/Hib (Infanrix Hexa) is currently funded for children up to 10 years (up to four doses) and up to four or five doses for children following immunosuppressive regimens (eg due to haematopoietic stem cell transplant, solid organ transplant or chemotherapy). The Committee noted that the current vaccination schedule is 3+0 at 6 weeks, 3 months and 5 months with DTaP booster at 4 years. The Committee noted that there is not currently a pertussis-containing dose in the second year of life, and considered that it would like to review the need for an additional dose at a future meeting.

Health Benefits

8.15. The Committee noted that Hexaxim is a fully liquid multi-antigen vaccine containing diphtheria, tetanus, pertussis (acellular, 2 component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed) antigens. The Committee noted that both Hexaxim and Infanrix Hexa contain pertussis filamentous Haemagglutinin (FHA) 25 mcg and pertussis toxoid (PT) 25 mcg, however, Infanrix Hexa also contains pertactin 8 mcg as a third pertussis antigen. The Committee noted that all other antigens contained in the two vaccines were the same except for the quantity of Hib polysaccharide (12 mcg Hexaxim vs 10 mcg Infanrix Hexa), diphtheria toxoid (>30 IU vs >20 IV, respectively) and that Infanrix Hexa contains aluminium phosphate.

8.16. The Committee considered that, if both vaccines were funded as part of the childhood immunisation schedule, at least one dose of Hexaxim would be administered concomitantly with the meningococcal B multicomponent vaccine (Bexsero) according to the immunisation schedule.

8.17. The Committee noted the following evidence from clinical trials and relevant studies that have been conducted since 2015:

- Vesikari et al. Pediatr Infect Dis J. 2017;36:87-93
- Prymula et al. Pediatr Infect Dis J. 2018;37:823-30
- Madhi et al. Hum Vaccin Immunother. 2019;15:658-68
- Madhi et al. Hum Vaccin Immunother. 2019;15:658-68
- Kosalaraksa et al. Hum Vaccin Immunother. 2018;14:1257-65
- Kosalaraksa et al. Hum Vaccin Immunother. 2018;14:1257-65
- Virta et al. Pediatr Infect Dis J. 2021;40:e28-30
- Vesikari et al. Vaccine. 2017;35:452-8
- Vesikari et al. Vaccine. 2018;36:8019-27
- Unpublished data from A3L00053-EXT trial
- Koen et al. Hum Vaccin Immunother. 2021;17:1770-8
- Martinelli et al. Vaccine. 2020;38:5148-53
- Casas et al. Conference presentation abstract. European Society for Paediatric Infectious Diseases - 40th Annual Meeting, Athens, Greece. May 09–13 2022. Abstract Nr. O028/#1823
- Lopez et al. Pediatr Infect Dis J. 2017;36:e272-82
- Martinón-Torres et al. Pediatr Infect Dis J. 2019;38:317-22

8.18. The Committee was made aware of evidence from a systematic literature search of published peer-reviewed head-to-head studies comparing any licensed hexavalent vaccine to another, including Hexaxim (trade name Hexyon in Europe) and Infanrix Hexa (Knuf et al. Vaccine. 2021;39:6025-36), including studies by Kosalaraksa et al, 2011; Aquino et al, 2012; Prymula et al, 2018; Vesikari et al, 2017 and Lopez et al, 2017). The Committee noted that there is no international consensus or guideline for non-inferiority of response to the pertussis vaccine components and considered it reasonable to consider a four-fold increase in coverage as reported by Knuf et al. The Committee was made aware that the authors reported similar results for two pertussis antigens (FHA and PT) with 2aP or 3aP and suggested a similar safety profile, although Hexaxim appeared more reactogenic than Infanrix Hexa (odds ratios of less than one for all safety signals except vomiting and any injection grade 3 reaction).

8.19. The Committee noted that essentially all studies met the required non-inferiority margins for primary and secondary endpoints including an international standard for response to HBV vaccination of >10 mIU/ml. The Committee noted that Hexaxim appears to provide statistically lower HBV protection to the international standard over time compared with Infanrix Hexa, however, considered this was a small effect and that there was uncertainty as to the clinical significance of it.

8.20. The Committee noted that international advice requested in 2015 regarding booster doses in the second year of life and ideally the entire evidence base (including that reviewed previously) would have been relevant to its review of Hexaxim. The Committee was made aware of the 2015 SAGE position statement on pertussis, which although silent on 2 vs 3 dose schedules, was of interest.

8.21. On balance, the Committee considered it would be clinically appropriate for DTPa-hepB-IPV-Hib (Hexaxim) to replace Infanrix Hexa in the childhood immunisation schedule provided that immunisation rates were at 95% or greater, but not at the present time based on current immunisation rates. The Committee considered that the consideration of the suitability of any change from Infanrix Hexa to Hexaxim on the childhood immunisation schedule should be deferred [redacted] (and evidence of

concomitant administration with the meningococcal B multicomponent vaccine Bexsero [real world, observational data of safety and immunogenicity], if it becomes available).

8.22. The Committee considered that Hexaxim would provide suitability benefits to the health system due to the fully liquid presentation in prefilled syringe, requiring no reconstitution, which has the potential to reduce the risk of dosing and clinical errors. The Committee considered that Hexaxim would not provide health benefits for any other New Zealand patient groups other than those currently eligible for Infanrix Hexa, nor would it provide any new health benefits for family, whānau or wider society over the currently funded vaccine.

8.23. The Committee considered that either 2+1 or 3+0 dose schedules could potentially be used, if Hexaxim were funded, given there is evidence to support use of both schedules. However, the Committee considered any change to the current hexavalent vaccine dosing schedule would need to be monitored closely, with the ability for further change based on such monitoring. The Committee reiterated its view that either the vaccine or of the dosing schedule could change, but not both, at the same time.

Suitability and Costs and Savings

8.24. The Committee considered that Hexaxim would be faster and easier to administer than Infanrix Hexa. The Committee had no other comments to make regarding the suitability or costs and savings of Hexaxim since the previous review in 2015.

Summary for Assessment

8.25. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for Hexaxim if it were to be funded in New Zealand for vaccination of infants from six weeks of age against DTPa-hepB-IPV-Hib who are currently eligible for Infanrix Hexa. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Patients who are currently eligible for Infanrix Hexa
Intervention	3 doses of Hexaxim at the following ages: • 6 weeks • 3 months • 5 months
Comparator(s)	3 doses of Infanrix Hexa at the following ages: • 6 weeks • 3 months • 5 months

Outcome(s)	Hexaxim is non-inferior to Infanrix Hexa in a 3+0 or 2+1 dosing schedule for protection against the following: • diphtheria • tetanus • Haemophilus influenzae type b • poliomyelitis • hepatitis B • pertussis (pending further direct evidence of efficacy against pertussis disease)
Table definitions: **P**opulation: the target population for the pharmaceutical; **I**ntervention: details of the intervention pharmaceutical; **C**omparator: details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); **O**utcomes: details the key therapeutic outcome(s) and source of outcome data.	