Coversheet on evidence assessment by ATAGI using the GRADE framework

Summary of key methods and decisions on evidence assessment using GRADE (Grading of Recommendations Assessment, Development and Evaluation) for developing ATAGI recommendations on the use of DT5aP-HBV-IPV-Hib(PRP-OMPC) (Vaxelis) in infants aged 6 weeks to 10 years for the Australian Immunisation Handbook

Background

- Hexavalent vaccination is currently undertaken in Australia under the National Immunisation Program at age 2, 4 and 6 months against diphtheria, tetanus, pertussis, polio, hepatitis B and *Haemophilus influenzae* type b.
- DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa; GSK) is the hexavalent vaccine currently used to deliver this program.
- DT5aP-HBV-IPV-Hib(PRP-OMPC) (Vaxelis; MCM) is a new vaccine that received a positive recommendation for NIP listing at the PBAC March 2022 meeting. It targets the same 6 conditions as Infanrix hexa, and is listed with the same dosing schedule.

Research question

Should infants aged 6 weeks to 10 years use DT5aP-HBV-IPV-Hib(PRP-TT) (Vaxelis) for primary vaccination in the same way as DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa)?

Table 1: Population, Intervention, Comparator, Outcomes (PICO) – DT5aP-HBV-IPV-Hib(PRP-OMPC) for primary vaccination vs DT3aP-HBV-IPV-Hib(PRP-TT) for primary vaccination, 6 weeks to 10 years of age

Population	Infants from 6 weeks to 10 years of age
Intervention	DT5aP-HBV-IPV-Hib(PRP-OMPC) (Vaxelis) as primary vaccination course
Comparator	DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa) as primary vaccination course
Outcomes	Critical • Immunogenicity at 5 months of age following a 3-dose primary course • Immunogenicity at 13 months of age following a 3-dose primary course and 1 dose of MenC/Hib(PRP-TT) at 12 months of age • Immunogenicity at 13 months of age following a 3-dose primary course and 1 booster dose at 12 months • Immunogenicity at 13 months of age following a 2-dose primary course and 1 booster dose at 11-12 months • Serious adverse events Important • Systemic adverse events • Local adverse events • Fever • Other AESI (Systemic and Local)

Abbreviations: AESI, adverse events special interest; SAE, serious adverse events

Literature search and selection

A definitive literature search to inform the GRADE assessment was performed by an information specialist based on the PICO question above, on 17/8/2022. The results of this literature search were provided to two independent reviewers for systematic assessment using the PICO inclusion criteria to determine final article selection. Details of the search methods are presented in Appendix A. The citations were selected for review if they met the following criteria:

- Study type: randomized controlled trial (RCT), observational study
- Population: infants aged 6 weeks to 10 years
- Intervention: DT5aP-HBV-IPV-Hib(PRP-OMPC) (Vaxelis) as primary vaccination course
- Comparator: DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa) as primary vaccination course
- Outcomes: Effectiveness, efficacy, immunogenicity, safety

Additional to the literature search, one unpublished study that met the inclusion criteria was identified. This study was included in the GRADE and since been published.

Risk of bias assessment

Risk of bias (RoB) was assessed for all selected studies using the standard GRADE criteria. Two assessors independently undertook this using the ROB 2.0 tool for randomised controlled trials (Appendix B).

Study inclusion criteria and rationale

In this initial GRADE assessment, a decision was made to focus on the primary infant schedule as it currently stands. If the use of Vaxelis is expanded in the future, further GRADE assessments may be undertaken to inform additional recommendations.

Table 3: Rationale for PICO and inclusion criteria

PICO	Rationale
Study type RCT	Vaccine immunogenicity has been assessed through RCTs. Comparison of vaccine safety between the intervention and comparator was undertaken through RCTs.
Population 6 weeks to 10 years old	Population anticipated to receive this vaccine are infants from 6 weeks to at least 6 months of age. No upper limit in TGA registration of Vaxelis. However, approved for PBAC for use up to 10 years of age.
Intervention DT5aP-HBV-IPV-Hib(PRP-OMPC) (Vaxelis) as primary vaccination course	New vaccine being introduced. PBAC approved for use in primary infant schedule at 2, 4 and 6 months of age, with catch-up to age 10 years.

Comparator DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa) as primary vaccination course	The intended use of Vaxelis is at the same time points and for the same population as Infanrix hexa. Other hexavalent vaccines targeting the same conditions are not currently routinely used in Australia.
Outcomes	Critical Immunogenicity at 5 months of age following a 3-dose primary course Immunogenicity at 13 months of age following a 3-dose primary course and a booster dose at 11-12 months Immunogenicity at 13 months of age following a 2-dose primary course and a booster dose at 11-12 months The ability of Vaxelis to provide early immunity against diseases of infancy is critical. Two of the three phase III RCTs give three doses of Vaxelis as the primary infant course at 2/3/4 months of age (V419-007 and the Oxford 6-in-1 Study), which was considered to be comparable to the proposed use of Vaxelis in Australia at 2/4/6 months. The persistence of immune response is also critical. Two of the RCTs of interest measured immunogenicity at 13 months, after a 3-dose primary course and a booster at 11-12 months (V419-007 and the Oxford 6-in-1 Study). It was felt that these trials were not comparable against the third manufacturer-sponsored RCT, where immunogenicity was also measured at 13 months, but after a 2-dose primary course and a booster at 11-12 months (V419-008). Therefore, two separate outcomes at 13 months of age were created, to account for these differences in the primary schedule.
	Critical: Safety Serious adverse events This outcome is critical for the assessment of vaccine safety.
	Important: Safety Specific inclusion of fever as an AESI as there is a higher risk of febrile convulsions in this age group.
	Note: some outcomes may be missing in GRADE projects due to lack of data from available studies.

Abbreviations: AESI, adverse events special interest; RCT, randomised controlled trial; SAE, serious adverse events

Appendix A: Literature Search Strategy

MEDLINE: (as at 17.08.22)	**EMBASE: (as at 17.08.22)**	**Cochrane Central Register of Controlled Trials, Issue 7 of 12, July 2022: (as at 17.08.22)**
Database: MEDLINE(R) All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946-current> Search Strategy: --- 1 ("DTaP3 IPV Hib HepB" or DTaP3-IPV-Hib-HepB or DTaP3IPVHibHepB).tw. (0) 2 ("DT3aP IPV Hib HepB" or DT3aP-IPV-Hib-HepB or DT3aPIPVHibHepB).tw. (0) 3 ("DT3aP IPV Hib HB" or DT3aP-IPV-Hib-HB or DT3aPIPVHibHB).tw. (0) 4 ("DTaP3 IPV Hib HBV" or DTaP3-IPV-Hib-HBV or DTaP3IPVHibHBV).tw. (0) 5 ("DT3aP IPV Hib HBV" or DT3aP-IPV-Hib-HBV or DT3aPIPVHibHBV).tw. (0) 6 ("DT3aP IPV Hib HB" or DT3aP-IPV-Hib-HB or DT3aPIPVHibHB).tw. (0) 7 (DTaP3 adj4 IPV adj4 Hib adj4 HepB).tw. (1) 8 (DTaP3 adj4 IPV adj4 Hib adj4 HBV).tw. (2) 9 (DTaP3 adj4 IPV adj4 Hib adj4 HB).tw. (1) 10 (Infanrix adj2 hexa$).tw. (79) 11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (80)	Database: Embase <1974 to 2022 August 15> Search Strategy: --- 1 ("DTaP3 IPV Hib HepB" or DTaP3-IPV-Hib-HepB or DTaP3IPVHibHepB).tw. (0) 2 ("DT3aP IPV Hib HepB" or DT3aP-IPV-Hib-HepB or DT3aPIPVHibHepB).tw. (0) 3 ("DT3aP IPV Hib HB" or DT3aP-IPV-Hib-HB or DT3aPIPVHibHB).tw. (0) 4 ("DTaP3 IPV Hib HBV" or DTaP3-IPV-Hib-HBV or DTaP3IPVHibHBV).tw. (0) 5 ("DT3aP IPV Hib HBV" or DT3aP-IPV-Hib-HBV or DT3aPIPVHibHBV).tw. (0) 6 ("DT3aP IPV Hib HB" or DT3aP-IPV-Hib-HB or DT3aPIPVHibHB).tw. (0) 7 (DTaP3 adj4 IPV adj4 Hib adj4 HepB).tw. (1) 8 (DTaP3 adj4 IPV adj4 Hib adj4 HBV).tw. (1) 9 (DTaP3 adj4 IPV adj4 Hib adj4 HB).tw. (1) 10 (Infanrix adj2 hexa$).tw. (311) 11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (312)	ID Search Hits #1 ("DTaP3 IPV Hib HepB" OR "DTaP3-IPV-Hib-HepB" OR DTaP3IPVHibHepB):ti,ab,kw 0 #2 ("DT3aP IPV Hib HepB" OR "DT3aP-IPV-Hib-HepB" OR DT3aPIPVHibHepB):ti,ab,kw 0 #3 ("DT3aP IPV Hib HB" or DT3aP-IPV-Hib-HB or DT3aPIPVHibHB):ti,ab,kw 0 #4 ("DTaP3 IPV Hib HBV" OR "DTaP3-IPV-Hib-HBV" OR DTaP3IPVHibHBV):ti,ab,kw 0 #5 ("DT3aP IPV Hib HBV" OR "DT3aP-IPV-Hib-HBV" OR DT3aPIPVHibHBV):ti,ab,kw 0 #6 ("DT3aP IPV Hib HB" or "DT3aP-IPV-Hib-HB" or DT3aPIPVHibHB):ti,ab,kw 0 #7 (DTaP3 NEAR/4 IPV NEAR/4 Hib NEAR/4 HepB):ti,ab,kw 0 #8 (DTaP3 NEAR/4 IPV NEAR/4 Hib NEAR/4 HBV):ti,ab,kw 0 #9 (DTaP3 NEAR/4 IPV NEAR/4 Hib NEAR/4 HB):ti,ab,kw 0 #10 (Infanrix NEAR/2 hexa*):ti,ab,kw 133 #11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 133 #12 ("DTaP5 IPV Hib HepB" OR "DTaP5-IPV-Hib-HepB" OR DTaP5IPVHibHepB):ti,ab,kw 4 #13 ("DTaP5 IPV Hib HBV" OR "DTaP5-IPV-Hib-HBV" OR DTaP5IPVHibHBV):ti,ab,kw 0 #14 ("DTaP5 IPV Hib HB" or "DTaP5-IPV-Hib-HB" or DTaP5IPVHibHB):ti,ab,kw 0 #15 ("DT5aP IPV Hib HepB" OR "DT5aP-IPV-Hib-HepB" OR DT5aPIPVHibHepB):ti,ab,kw 0

12 ("DTaP5 IPV Hib HepB" or DTaP5-IPV-Hib-HepB or DTaP5IPVHibHepB).tw. (7) 13 ("DTaP5 IPV Hib HBV" or DTaP5-IPV-Hib-HBV or DTaP5IPVHibHBV).tw. (0) 14 ("DTaP5 IPV Hib HB" or DTaP5-IPV-Hib-HB or DTaP5IPVHibHB).tw. (0) 15 ("DT5aP IPV Hib HepB" or DT5aP-IPV-Hib-HepB or DT5aPIPVHibHepB).tw. (0) 16 ("DT5aP IPV Hib HBV" or DT5aP-IPV-Hib-HBV or DT5aPIPVHibHBV).tw. (0) 17 ("DT5aP IPV Hib HB" or DT5aP-IPV-Hib-HB or DT5aPIPVHibHB).tw. (0) 18 (DTaP5 adj4 IPV adj4 Hib adj4 HepB).tw. (8) 19 (DTaP5 adj4 IPV adj4 Hib adj4 HBV).tw. (2) 20 (DTaP5 adj4 IPV adj4 Hib adj4 HB).tw. (7) 21 vaxelis$.tw. (7) 22 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (22) 23 11 and 22 (9) 24 exp Immunogenicity, Vaccine/ (3106) 25 immunogen$.tw. (86088) 26 exp Antibodies, Bacterial/ (52028) 27 exp Antibodies, Viral/ (118526) 28 exp Antibody Formation/ (63184) 29 (antibod$ adj2 (respons$ or form$)).tw. (60013) 30 (immun$ adj2 (respon$ or protect$)).tw. (338600) 31 exp Seroconversion/ (1104) 32 seroconver$.tw. (20790) 33 seroprotect$.tw. (1901)	12 ("DTaP5 IPV Hib HepB" or DTaP5-IPV-Hib-HepB or DTaP5IPVHibHepB).tw. (7) 13 ("DTaP5 IPV Hib HBV" or DTaP5-IPV-Hib-HBV or DTaP5IPVHibHBV).tw. (0) 14 ("DTaP5 IPV Hib HB" or DTaP5-IPV-Hib-HB or DTaP5IPVHibHB).tw. (0) 15 ("DT5aP IPV Hib HepB" or DT5aP-IPV-Hib-HepB or DT5aPIPVHibHepB).tw. (0) 16 ("DT5aP IPV Hib HBV" or DT5aP-IPV-Hib-HBV or DT5aPIPVHibHBV).tw. (0) 17 ("DT5aP IPV Hib HB" or DT5aP-IPV-Hib-HB or DT5aPIPVHibHB).tw. (0) 18 (DTaP5 adj4 IPV adj4 Hib adj4 HepB).tw. (8) 19 (DTaP5 adj4 IPV adj4 Hib adj4 HBV).tw. (2) 20 (DTaP5 adj4 IPV adj4 Hib adj4 HB).tw. (8) 21 vaxelis$.tw. (23) 22 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (36) 23 11 and 22 (17) 24 exp vaccine immunogenicity/ (5395) 25 immunogen$.tw. (112161) 26 exp bacterium antibody/ (26542) 27 exp virus antibody/ (101248) 28 exp antibody production/ (60938) 29 (antibod$ adj2 (respons$ or form$)).tw. (67938) 30 (immun$ adj2 (respon$ or protect$)).tw. (435606) 31 exp seroconversion/ (27072) 32 seroconver$.tw. (27045) 33 seroprotect$.tw. (2385)	#16 ("DT5aP IPV Hib HBV" OR "DT5aP-IPV-Hib-HBV" OR DT5aPIPVHibHBV):ti,ab,kw 0 #17 ("DT5aP IPV Hib HB" or "DT5aP-IPV-Hib-HB" or DT5aPIPVHibHB):ti,ab,kw 0 #18 (DTaP5 NEAR/4 IPV NEAR/4 Hib NEAR/4 HepB):ti,ab,kw 0 #19 (DTaP5 NEAR/4 IPV NEAR/4 Hib NEAR/4 HBV):ti,ab,kw 1 #20 (DTaP5 NEAR/4 IPV NEAR/4 Hib NEAR/4 HB):ti,ab,kw 0 #21 vaxelis*:ti,ab,kw10 #22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 14 #23 #11 AND #22 5 #24 MeSH descriptor: [Immunogenicity, Vaccine] explode all trees 519 #25 immunogen*:ti,ab,kw 15177 #26 MeSH descriptor: [Antibodies, Bacterial] explode all trees 1705 #27 MeSH descriptor: [Antibodies, Viral] explode all trees 3893 #28 MeSH descriptor: [Antibody Formation] explode all trees 1035 #29 (antibod* NEAR/2 (respons* OR form*)):ti,ab,kw 5313 #30 (immun* NEAR/2 (respon* OR protect*)):ti,ab,kw 16018 #31 MeSH descriptor: [Seroconversion] explode all trees 110 #32 seroconver*:ti,ab,kw 4323 #33 seroprotect*:ti,ab,kw 1299 #34 MeSH descriptor: [Treatment Outcome] explode all trees 153195 #35 efficac*:ti,ab,kw 401985 #36 effective*:ti,ab,kw 377682 #37 MeSH descriptor: [Safety] explode all trees 4145

34 exp Treatment Outcome/ (1206245) 35 efficac$.tw. (1016230) 36 effective$.tw. (2343787) 37 exp Safety/ (87633) 38 exp Safety-Based Drug Withdrawals/ (414) 39 exp "Drug-Related Side Effects and Adverse Reactions"/ (128239) 40 exp Product Surveillance, Postmarketing/ (17670) 41 exp Drug Evaluation/ (42040) 42 exp Adverse Drug Reaction Reporting Systems/ (8558) 43 (adverse adj2 (effect$ or event$)).tw. (424595) 44 (safe or safety or aefi or aesi).tw. (949883) 45 ((post marketing or post-marketing or postmarketing or post licensure or post-licensure or postlicensure) adj2 (surveillance or monitor$)).tw. (3456) 46 exp Fever/ (46597) 47 (pyrexia$ or fever$).tw. (199644) 48 ((raise$ or rise$) adj3 temperature$).tw. (10306) 49 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 (5336887) 50 23 and 49 (9)	34 exp drug efficacy/ (966181) 35 efficac$.tw. (1474564) 36 effective$.tw. (3041384) 37 exp drug safety/ (503749) 38 exp postmarketing surveillance/ (38094) 39 exp drug surveillance program/ (26605) 40 exp adverse drug reaction/ (590473) 41 (adverse adj2 (effect$ or event$)).tw. (664884) 42 (safe or safety or aefi or aesi).tw. (1428477) 43 ((post marketing or post-marketing or postmarketing or post licensure or post-licensure or postlicensure) adj2 (surveillance or monitor$)).tw. (5272) 44 exp fever/ (293659) 45 (pyrexia$ or fever$).tw. (273164) 46 ((raise$ or rise$) adj3 temperature$).tw. (11158) 47 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 (6706914) 48 23 and 47 (16)	#38 MeSH descriptor: [Safety-Based Drug Withdrawals] explode all trees 11 #39 MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees 3879 #40 MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees 215 #41 MeSH descriptor: [Drug Evaluation] explode all trees 5751 #42 MeSH descriptor: [Adverse Drug Reaction Reporting Systems] explode all trees 95 #43 (adverse NEAR/2 (effect* OR event*)):ti,ab,kw 278763 #44 (safe OR safety OR aefi OR aesi):ti,ab,kw 304630 #45 ((post marketing OR post-marketing OR postmarketing OR post licensure OR post-licensure OR postlicensure) NEAR/2 (surveillance OR monitor*)):ti,ab,kw 1279 #46 MeSH descriptor: [Fever] explode all trees2208 #47 (pyrexia* OR fever*):ti,ab,kw 22591 #48 ((raise* OR rise*) NEAR/3 temperature*):ti,ab,kw 380 #49 #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 900363 #50 #23 AND #49 5

Appendix B: Risk of Bias: ROB 2.0

Intention-to-treat

Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
Vaxelis_IO1_00	Vesikari	Vaxelis	Infanrix hexa	Immunogenicity 1 5 months 3 doses	1	+	+	+	+	+	+
Vaxelis_IO1_6ir	Snape	Vaxelis	Infanrix hexa	Immunogenicity 1 5 months 3 doses	1	+	+	+	+	+	+
Vaxelis_IO2_00	Vesikari	Vaxelis	Infanrix hexa	Immunogenicity 2 13 months 3 plus 1 doses	1	+	+	+	+	+	+
Vaxelis_IO2_6ir	Snape	Vaxelis	Infanrix hexa	Immunogenicity 2 13 months 3 plus 1 doses	1	+	+	+	+	+	+
Vaxelis_IO3_00	Silfverdal	Vaxelis	Infanrix hexa	Immunogenicity 3 13 months 2 plus 1 doses	1	+	+	+	+	+	+

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Intention-to-treat

Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
Vaxelis_S1_008	Silfverdal	Vaxelis	Infanrix hexa	Safety 1 SAEs	1	+	+	+	+	+	+
Vaxelis_S1_007	Vesikari	Vaxelis	Infanrix hexa	Safety 1 SAEs	1	+	+	+	+	+	+
Vaxelis_S1_6in1	Snape	Vaxelis	Infanrix hexa	Safety 1 SAEs	1	+	+	+	-	!	-
Vaxelis_S2_008	Silfverdal	Vaxelis	Infanrix hexa	Safety 2 Systemic AEs	1	+	+	+	+	+	+
Vaxelis_S2_007	Vesikari	Vaxelis	Infanrix hexa	Safety 2 Systemic AEs	1	+	+	+	+	+	+
Vaxelis_S2_6in1	Snape	Vaxelis	Infanrix hexa	Safety 2 Systemic AEs	1	+	+	+	!	+	!
Vaxelis_S3_008	Silfverdal	Vaxelis	Infanrix hexa	Safety 3 Local AEs	1	+	+	+	+	+	+
Vaxelis_S3_007	Vesikari	Vaxelis	Infanrix hexa	Safety 3 Local AEs	1	+	+	+	+	+	+
Vaxelis_S4_008	Silfverdal	Vaxelis	Infanrix hexa	Safety 4 Fever	1	+	+	+	+	+	+
Vaxelis_S4_007	Vesikari	Vaxelis	Infanrix hexa	Safety 4 Fever	1	+	+	+	+	+	+
Vaxelis_S4_6in1	Snape	Vaxelis	Infanrix hexa	Safety 4 Fever	1	+	+	+	-	+	!
Vaxelis_S5_008	Silfverdal	Vaxelis	Infanrix hexa	Safety 5 AESIs	1	+	+	+	+	+	+
Vaxelis_S5_007	Vesikari	Vaxelis	Infanrix hexa	Safety 5 AESIs	1	+	+	+	+	+	+
Vaxelis_S5_6in1	Snape	Vaxelis	Infanrix hexa	Safety 5 AESIs	1	+	+	+	-	+	!

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result