NCIRS is conducting GRADE in support of ATAGI and making pilot results available on the NCIRS website. Please read this material as a supplement to the Australian Immunisation Handbook

Summary of findings: DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) compared to DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa) in infants and children aged 6 weeks to 10 years for primary vaccination

Patient or population: infants and children aged 6 weeks to 10 years for primary vaccination
Intervention: DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis)
Comparison: DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa)

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI) Difference between DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) and (infanrix hexa)	Certainty	Comments
CRITICAL OUTCOMES				
Immunogenicity at 5 months after 3 primary doses (2 / 3 / 4 months) assessed with: percentage participants with antibody titres above cutoff values AND geometric mean concentrations follow-up: 1 month (2 RCTs)		**Table 1A:** Endpoints reported as percentage of participants with antibody titres above pre-defined thresholds **Table 1B:** Endpoints reported as geometric mean concentrations (GMCs)	⊕⊕⊕⊕ High	DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) results in little to no difference in immunogenicity at 5 months of age after 3 primary doses compared to DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa). Ref: 1,2

Table 1A: Endpoints reported as percentage of participants with antibody titres above pre-defined thresholds

			Vaxelis			Infanrix hexa			Comparison			
Antigen	Measurement	Study	n	Point estimate	95% CI	n	Point estimate	95% CI	Difference in point estimate	95% CI	Non-inferiority threshold	Non-inferiority met
Diphtheria toxoid	% titre ≥0.01 IU/ml	Vesikari	541	99.82	98.98 to 100.00	516	99.81	98.93 to 100.00	0.01		-10	Yes
Tetanus toxoid	% titre ≥0.01 IU/ml	Vesikari	538	100.00	99.32 to 100.00	519	100.00	99.29 to 100.00	0		-5	Yes
Poliovirus type 1	% NAb ≥1:8 dilution	Vesikari	547	100.00	99.33 to 100.00	527	99.81	98.95 to 100.00	0.19		-5	Yes
Poliovirus type 2	% NAb ≥1:8 dilution	Vesikari	546	99.82	98.99 to 100.00	528	99.62	98.64 to 99.95	0.20		-5	Yes
Poliovirus type 3	% NAb ≥1:8 dilution	Vesikari	545	100.00	99.33 to 100.00	525	100.00	99.30 to 100.00	0		-5	Yes
Hib PRP	% titre ≥0.15 µg/ml	Vesikari	541	98.36	96.92 to 99.25	453	86.95	83.75 to 89.72	11.41		-10	Yes
		Oxford	79	100.00		84	96.43		3.57	-1.63 to 8.77	-10	Yes

Table 1B: Endpoints reported as geometric mean concentrations (GMCs)

			Vaxelis			Infanrix hexa			Comparison	
Antigen	Measurement	Study	n	Point estimate	95% CI	n	Point estimate	95% CI	Geometric Mean Ratio	95% CI
Diphtheria toxoid	GMC	Vesikari	542	0.11	0.10 to 0.12	517	0.11	0.11 to 0.12	1.00	
		Oxford	85	0.24	0.19 to 0.29	87	0.47	0.39 to 0.56	0.51[A]	0.39 to 0.67
Tetanus toxoid	GMC	Vesikari	538	0.70	0.67 to 0.73	519	0.53	0.51 to 0.56	1.32[B]	
		Oxford	85	2.81	2.38 to 3.31	87	1.49	1.27 to 1.75	1.88[B]	1.50 to 2.36
Hib PRP	GMC	Vesikari	550	3.90	3.46 to 4.41	521	0.65	0.59 to 0.73	6.00[B]	
		Oxford	85	20.34	14.58 to 28.37	87	0.87	0.66 to 1.16	23.25[B,C]	15.11 to 35.78
Hep B sAg	GMC	Vesikari	510	234.31	210.11 to 261.29	483	242.22	214.29 to 273.80	0.97	
		Oxford	52	244.96	165.52 to 362.52	53	341.41	263.35 to 442.60	0.72	0.45 to 1.14
Pertussis PT	GMC	Vesikari	534	129.58	123.92 to 135.50	514	83.66	79.54 to 87.99	1.55[B]	
		Oxford	85	54.19	45.73 to 64.21	86	35.69	31.17 to 40.86	1.49[B]	1.20 to 1.84
Pertussis FHA	GMC	Vesikari	533	49.51	46.90 to 52.27	513	96.80	91.70 to 102.18	0.51[A]	
		Oxford	79	5.65	4.80 to 6.64	84	19.63	16.56 to 23.27	0.28[A]	0.22 to 0.36
Pertussis PRN	GMC	Vesikari	534	46.76	42.72 to 51.17	514	77.79	72.63 to 83.32	0.60[A]	
		Oxford	83	37.42	31.10 to 45.03	85	48.54	40.35 to 58.39	0.77	0.59 to 1.00

Summary of findings: DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) compared to DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa) in infants and children aged 6 weeks to 10 years for primary vaccination

Patient or population: infants and children aged 6 weeks to 10 years for primary vaccination
Intervention: DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis)
Comparison: DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa)

<table>
<tr><th rowspan="2">Outcome
№ of participants
(studies)</th><th rowspan="2">Relative effect
(95% CI)</th><th colspan="2">Anticipated absolute effects (95% CI)

Difference between DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) and (infanrix hexa)</th><th rowspan="2">Certainty</th><th rowspan="2">Comments</th></tr>
<tr></tr>
<tr>
<td>Immunogenicity at 13 months after 3 primary doses and 1 dose of Hib(PRP-TT)/MenC given at 12 months of age (2 / 3 / 4 month primary schedule) assessed with: percentage participants with antibody titres above cutoff values AND geometric mean concentrations
follow-up: 1 month
(1 RCT)</td>
<td></td>
<td colspan="2">
Table 2A: Endpoints reported as percentage of participants with antibody titres above pre-defined thresholds
<table>
<tr><th></th><th></th><th></th><th colspan="2">Vaxelis</th><th colspan="2">Infanrix hexa</th><th colspan="2">Comparison</th></tr>
<tr><th>Antigen</th><th>Measurement</th><th>Study</th><th>n</th><th>Point estimate</th><th>n</th><th>Point estimate</th><th>Difference in point estimate</th><th>95% CI</th></tr>
<tr><td>Diphtheria toxoid</td><td>% titre ≥0.1 IU/ml</td><td>Oxford</td><td>79</td><td>96.2</td><td>84</td><td>97.62</td><td>-1.42</td><td>-7.97 to 5.14</td></tr>
<tr><td>Tetanus toxoid</td><td>% titre ≥0.1 IU/ml</td><td>Oxford</td><td>79</td><td>100.00</td><td>84</td><td>100.00</td><td>0</td><td>0</td></tr>
<tr><td>Hib PRP</td><td>% titre ≥1.00 µg/ml</td><td>Oxford</td><td>79</td><td>100</td><td>84</td><td>96.43</td><td>3.57</td><td>-1.63 to 8.77</td></tr>
<tr><td>Hep B sAg</td><td>% titre ≥10 IU/ml</td><td>Oxford</td><td>60</td><td>91.67</td><td>62</td><td>93.55</td><td>-1.88</td><td>-12.81 to 9.05</td></tr>
</table>
Table 2B: Endpoints reported as geometric mean concentrations (GMCs)
<table>
<tr><th></th><th></th><th></th><th colspan="3">Vaxelis</th><th colspan="3">Infanrix hexa</th><th colspan="2">Comparison</th></tr>
<tr><th>Antigen</th><th>Measurement</th><th>Study</th><th>n</th><th>Point estimate</th><th>95% CI</th><th>n</th><th>Point estimate</th><th>95% CI</th><th>Geometric Mean Ratio</th><th>95% CI</th></tr>
<tr><td>Hep B sAg</td><td>GMC</td><td>Oxford</td><td>60</td><td>75.00</td><td>51.07 to 110.14</td><td>62</td><td>148.90</td><td>102.07 to 217.23</td><td>0.50[A]</td><td>0.30 to 0.86</td></tr>
<tr><td>Hib PRP</td><td>GMC</td><td>Oxford</td><td>79</td><td>88.07</td><td>66.38 to 116.85</td><td>84</td><td>15.21</td><td>10.89 to 21.25</td><td>5.79[B]</td><td>3.75 to 8.94</td></tr>
<tr><td>Pertussis PT</td><td>GMC</td><td>Oxford</td><td>79</td><td>8.01</td><td>6.56 to 9.78</td><td>84</td><td>9.10</td><td>7.55 to 10.97</td><td>0.88</td><td>0.67 to 1.16</td></tr>
<tr><td>Pertussis FHA</td><td>GMC</td><td>Oxford</td><td>79</td><td>5.65</td><td>4.80 to 6.64</td><td>84</td><td>19.63</td><td>16.56 to 23.27</td><td>0.28[A]</td><td>0.22 to 0.36</td></tr>
<tr><td>Pertussis PRN</td><td>GMC</td><td>Oxford</td><td>79</td><td>8.68</td><td>6.92 to 10.89</td><td>84</td><td>6.87</td><td>5.49 to 8.59</td><td>1.28</td><td>0.93 to 1.76</td></tr>
</table>
</td>
<td>⊕⊕⊕◯
Moderate[a]</td>
<td>DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) likely results in little to no difference in immunogenicity at 5 months of age after 3 primary doses compared to DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa). Ref: 2</td>
</tr>
</table>

Summary of findings: DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) compared to DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa) in infants and children aged 6 weeks to 10 years for primary vaccination

Patient or population: infants and children aged 6 weeks to 10 years for primary vaccination
Intervention: DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis)
Comparison: DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa)

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI) Difference between DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) and (infanrix hexa)	Certainty	Comments

Table 3A: Endpoints reported as percentage of participants with antibody titres above pre-defined thresholds

			Vaxelis			Infanrix hexa			Comparison		
Antigen	Measurement	Study	n	Point estimate	95% CI	n	Point estimate	95% CI	Difference in point estimate	NI threshold	NI met
Diphtheria toxoid	% titre ≥0.1 IU/ml	Vesikari	531	99.81	98.96 to 100	508	100.00	99.28 to 100	-0.19	Not defined	n/a
Tetanus toxoid	% titre ≥0.1 IU/ml	Vesikari	528	100.00	99.30 to 100	504	100.00	99.27 to 100	0	Not defined	n/a
Poliovirus type 1	% NAb ≥1:8 dilution	Vesikari	538	99.81	98.97 to 100	524	100.00	99.30 to 100	-0.19	Not defined	n/a
Poliovirus type 2	% NAb ≥1:8 dilution	Vesikari	538	100.00	99.32 to 100	524	100.00	99.30 to 100	0	Not defined	n/a
Poliovirus type 3	% NAb ≥1:8 dilution	Vesikari	541	100.00	99.32 to 100	523	99.81	98.94 to 100	0.19	Not defined	n/a
Hib PRP	% titre ≥1.00 µg/ml	Vesikari	439	94.99	92.51 to 96.83	432	97.69	95.78 to 98.88	-2.70	Not defined	n/a
Hep B sAg	% titre ≥10 IU/ml	Vesikari	551	99.64	98.70 to 99.96	531	99.06	97.82 to 99.69	0.58	-10	Yes
Pertussis PT	% "seroresponse"[A]	Vesikari	543	99.82	98.98 to 100	523	98.34	97.01 to 99.34	1.48	-10	Yes
Pertussis FHA	% "seroresponse"[A]	Vesikari	542	97.23	95.48 to 98.44	523	99.81	98.94 to 100	-2.58	-10	Yes
Pertussis PRN	% "seroresponse"[A]	Vesikari	543	98.90	97.61 to 99.59	523	98.85	97.52 to 99.58	0.05	-10	Yes

Table 3B: Endpoints reported as geometric mean concentrations (GMCs)

			Vaxelis			Infanrix hexa			Comparison
Antigen	Measurement	Study	n	Point estimate	95% CI	n	Point estimate	95% CI	Geometric Mean Ratio
Hep B sAg	GMC	Vesikari	551	2984.26	2649.79 to 3360.95	531	3369.05	2933.67 to 3869.03	0.89
Hib PRP	GMC	Vesikari	439	6.79	6.11 to 7.54	432	21.39	18.77 to 24.37	0.32[A]
Pertussis PT	GMC	Vesikari	548	196.81	186.52 to 207.67	529	90.69	85.82 to 95.84	2.17[B]
Pertussis FHA	GMC	Vesikari	547	121.59	115.68 to 127.80	529	196.53	186.88 to 206.67	0.62[A]
Pertussis PRN	GMC	Vesikari	548	166.67	155.40 to 178.75	529	182.08	168.93 to 196.24	0.92

Immunogenicity at 13 months after 3 primary doses and 1 booster dose (2 / 3 / 4 months + 12 months) assessed with: percentage participants with antibody titres above cutoff values AND geometric mean concentrations follow-up: 1 month (1 RCT)			⊕⊕⊕⊕ High	DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) results in little to no difference in immunogenicity at 5 months of age after 3 primary doses compared to DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa). Ref: 1

Summary of findings: DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) compared to DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa) in infants and children aged 6 weeks to 10 years for primary vaccination

Patient or population: infants and children aged 6 weeks to 10 years for primary vaccination
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<tr><th rowspan="2">Outcome
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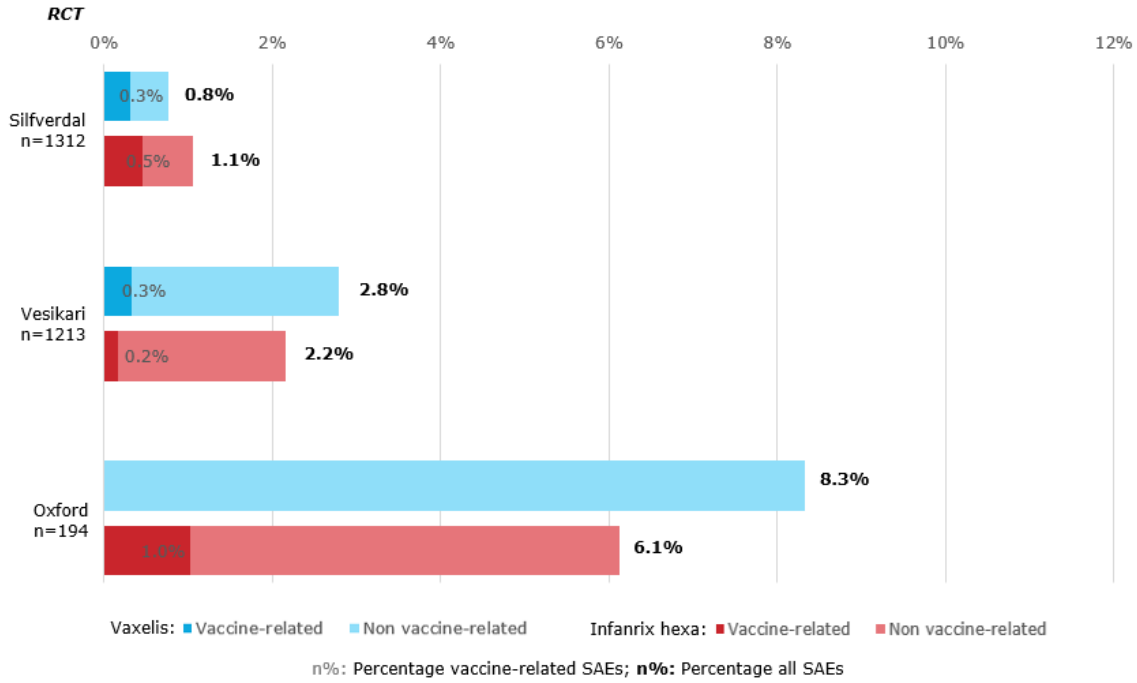
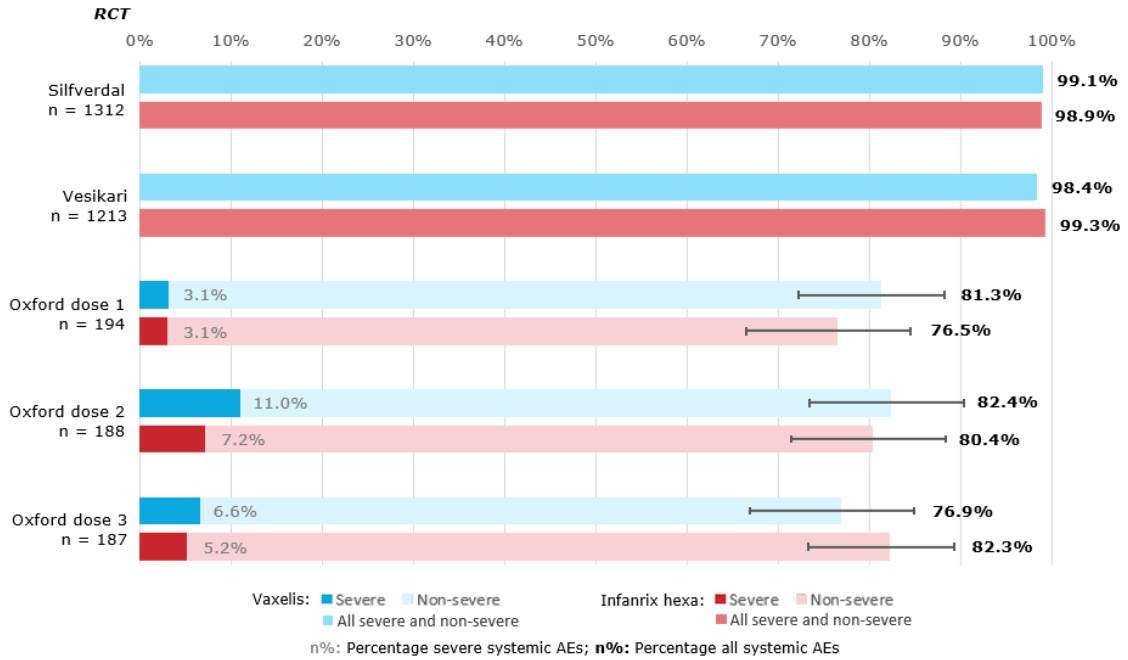
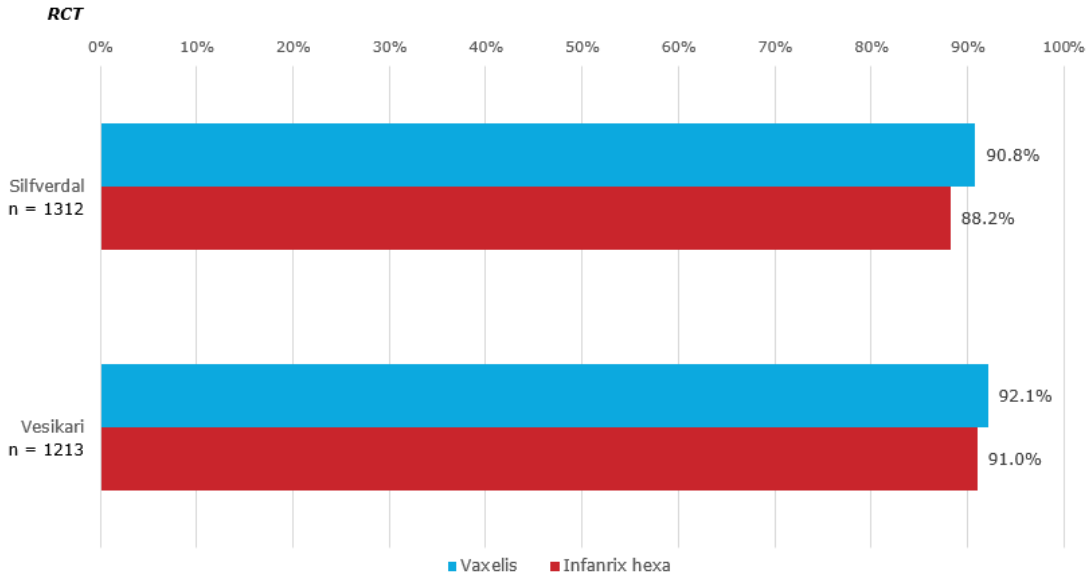
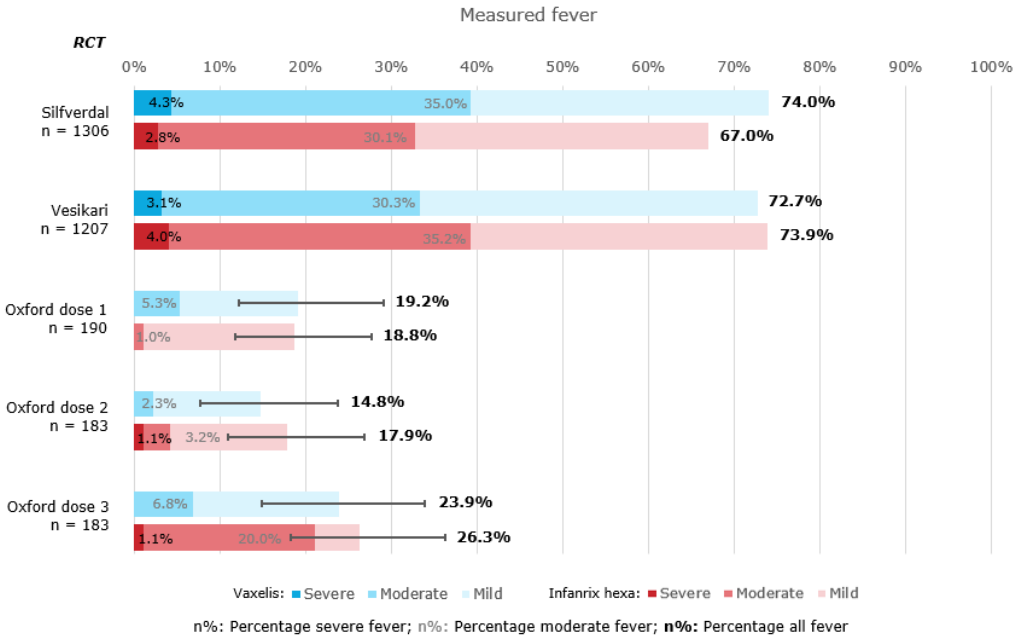
(studies)</th><th rowspan="2">Relative effect
(95% CI)</th><th colspan="2">Anticipated absolute effects (95% CI)

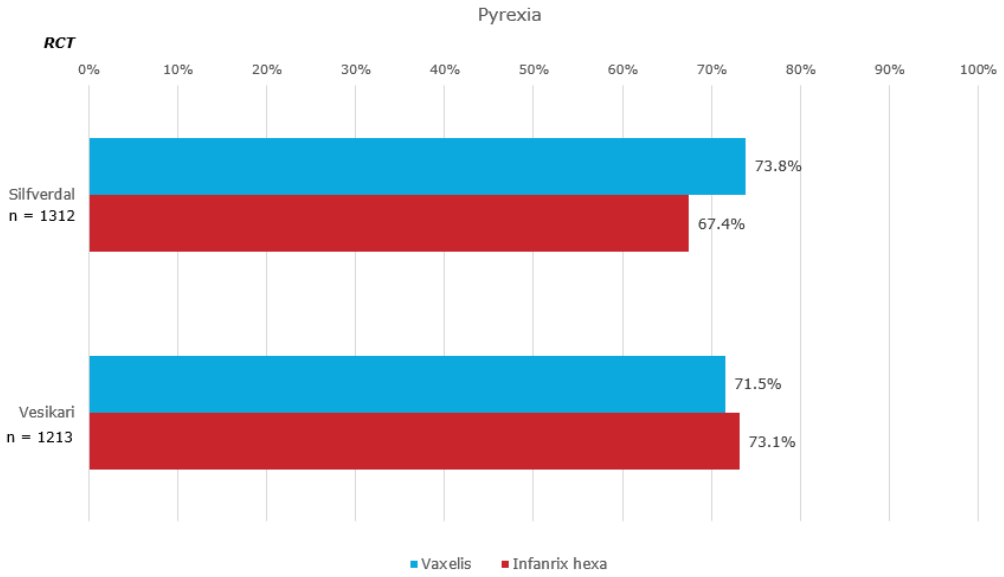
Difference between DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) and (infanrix hexa)</th><th rowspan="2">Certainty</th><th rowspan="2">Comments</th></tr>
<tr></tr>
<tr>
<td>Immunogenicity at 13 months after 2 primary doses and 1 booster dose (2 / 4 months + 11-12 months) assessed with: percentage participants with antibody titres above cutoff values
follow-up: 1 month
(1 RCT)</td>
<td></td>
<td colspan="2">
Table 4: Endpoints reported as percentage of participants with antibody titres above pre-defined thresholds
<table>
<tr><th></th><th></th><th></th><th colspan="3">Vaxelis</th><th colspan="3">Infanrix hexa</th><th colspan="3">Comparison</th></tr>
<tr><th>Antigen</th><th>Measurement</th><th>Study</th><th>n</th><th>Point estimate</th><th>95% CI</th><th>n</th><th>Point estimate</th><th>95% CI</th><th>Difference in point estimate</th><th>NI threshold</th><th>NI met</th></tr>
<tr><td>Diphtheria toxoid</td><td>% titre ≥0.1 IU/ml</td><td>Silfverdal</td><td>590</td><td>98.62</td><td>97.35 to 99.41</td><td>578</td><td>99.83</td><td>99.04 to 100</td><td>-1.21</td><td>-10</td><td>Yes</td></tr>
<tr><td>Tetanus toxoid</td><td>% titre ≥0.1 IU/ml</td><td>Silfverdal</td><td>589</td><td>99.83</td><td>99.06 to 100</td><td>577</td><td>100</td><td>99.36 to 100</td><td>-0.17</td><td>-5</td><td>Yes</td></tr>
<tr><td>Poliovirus type 1</td><td>% NAb ≥1:8 dilution</td><td>Silfverdal</td><td>591</td><td>99.32</td><td>98.28 to 99.82</td><td>580</td><td>99.83</td><td>99.04 to 100</td><td>-0.51</td><td>-5</td><td>Yes</td></tr>
<tr><td>Poliovirus type 2</td><td>% NAb ≥1:8 dilution</td><td>Silfverdal</td><td>591</td><td>99.83</td><td>99.06 to 100</td><td>579</td><td>100</td><td>99.36 to 100</td><td>-0.17</td><td>-5</td><td>Yes</td></tr>
<tr><td>Poliovirus type 3</td><td>% NAb ≥1:8 dilution</td><td>Silfverdal</td><td>590</td><td>99.49</td><td>98.52 to 99.90</td><td>579</td><td>99.65</td><td>98.76 to 99.93</td><td>-0.16</td><td>-5</td><td>Yes</td></tr>
<tr><td>Hib PRP</td><td>% titre ≥1.00 µg/ml</td><td>Silfverdal</td><td>454</td><td>89.87</td><td>86.72 to 92.49</td><td>478</td><td>91.00</td><td>88.07 to 93.41</td><td>-1.13</td><td>-10</td><td>Yes</td></tr>
<tr><td>Hep B sAg</td><td>% titre ≥10 IU/ml</td><td>Silfverdal</td><td>377</td><td>98.14</td><td>96.21 to 99.25</td><td>391</td><td>98.27</td><td>97.04 to 99.58</td><td>-0.13</td><td>-10</td><td>Yes</td></tr>
<tr><td>Pertussis PT</td><td>% “seroresponse”</td><td>Silfverdal</td><td>566</td><td>99.12</td><td>97.95 to 99.71</td><td>561</td><td>99.64</td><td>98.72 to 99.96</td><td>-0.52</td><td>-10</td><td>Yes</td></tr>
<tr><td>Pertussis FHA</td><td>% “seroresponse”</td><td>Silfverdal</td><td>582</td><td>97.42</td><td>95.78 to 98.55</td><td>571</td><td>99.12</td><td>97.97 to 99.72</td><td>-1.70</td><td>-10</td><td>Yes</td></tr>
<tr><td>Pertussis PRN</td><td>% “seroresponse”</td><td>Silfverdal</td><td>582</td><td>96.91</td><td>95.16 to 98.16</td><td>572</td><td>98.25</td><td>96.81 to 99.16</td><td>-1.34</td><td>-10</td><td>Yes</td></tr>
</table>
</td>
<td>⨁⨁⨁⨁
High</td>
<td>DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) results in little to no difference in immunogenicity at 13 months of age after 2 primary doses and 1 booster dose compared to DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa). Ref: 3</td>
</tr>
</table>

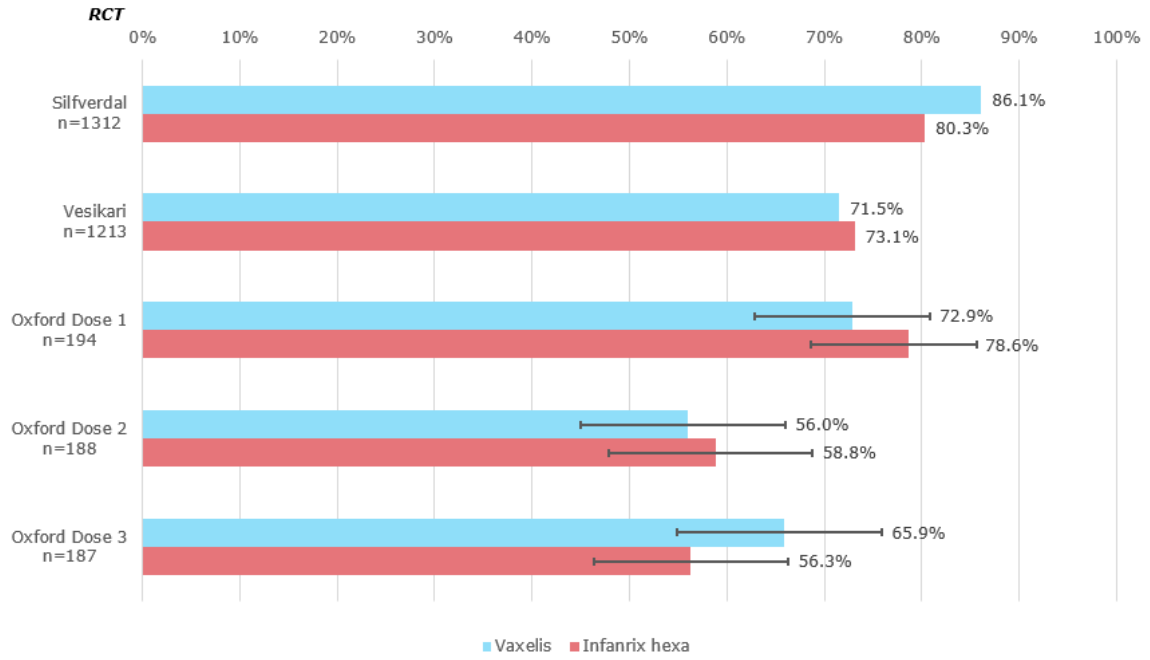
Serious Adverse Events (SAEs) assessed with: symptom diaries follow-up: dose 1 to 1 month after final dose (3 RCTs)		⨁⨁⨁⨁ High[b]	DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) results in little to no difference in serious adverse events compared to DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa). Ref: 1-3

IMPORTANT OUTCOMES			
Systemic Adverse Events assessed with: symptom diaries follow-up: range 5 days to 15 days (3 RCTs)		⊕⊕⊕◯ Moderate[b]	DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) likely results in little to no difference in systemic adverse events compared to DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa). Ref: 1-3

Local Adverse Events assessed with: symptom diaries follow-up: range 5 days to 15 days (2 RCTs)		⨁⨁⨁◯ Moderate[b]	DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) likely results in little to no difference in local adverse events compared to DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa). Ref: 1,3	

Fever assessed with: daily temperature measurements AND symptom diaries follow-up: range 5 days to 15 days (3 RCTs)		⊕⊕⊕◯ Moderate[b]	DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) likely results in little to no difference in fever compared to DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa). Ref: 1-3


Pyrexia
RCT
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Silfverdal
n = 1312
73.8%
67.4%
Vesikari
n = 1213
71.5%
73.1%
Vaxelis
Infanrix hexa

Adverse Event of Special Interest: Somnolence / Drowsiness assessed with: symptom diaries follow-up: range 5 days to 15 days (3 RCTs)		⊕⊕⊕◯ Moderate[b]	DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) likely results in little to no difference in fever compared to DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa). Ref: 1-3

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
The number of participants (n) for each antigen varied within each study, due to differences in the number of valid laboratory results for individual antigens.

CI: confidence interval; **GMC:** geometric mean concentration; **GMR:** geometric mean ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. The Oxford study is a small study with 194 enrolled participants in total.
b. Both the Silfverdal and Vesikari studies pool safety outcome data between the 3 infant doses and the toddler booster dose.

Evidence Profile: Summary of findings: DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis) compared to DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa) in infants and children aged 6 weeks to 10 years for primary vaccination

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis)	DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa)	Relative (95% CI)	Absolute (95% CI)		
CRITICAL OUTCOMES												
Immunogenicity at 5 months after 3 primary doses (follow-up: 1 month; assessed with: percentage participants with antibody titres above cutoff values AND geometric mean concentrations)												
2	randomised trials	not serious	not serious	not serious	not serious	none	Vesikari (2017)[1]: Selected endpoints **Percentage participants achieving antibody titres above set cutoff values:** **Diphtheria, tetanus, polio 1 / 2 / 3:** met pre-determined non-inferiority criteria with no statistical difference between Vaxelis and Infanrix hexa groups. **Hib PRP:** met pre-determined non-inferiority criteria, significantly higher percentage of Vaxelis group with antibody titres ≥0.15µg/mL. **GMCs and GMRs:** **Hib PRP:** GMR favours Vaxelis (6.00) with non-overlapping 95% CIs for Vaxelis and Infanrix hexa GMCs. **Hepatitis B**: No statistical difference in GMCs between Vaxelis and Infanrix hexa groups. **Pertussis FHA, PRN**: GMCs significantly lower in Vaxelis group. **Pertussis PT:** GMCs significantly higher in Vaxelis group. Oxford (Unpublished)[2]: Selected endpoints **Percentage participants achieving antibody titres above set cutoff values:** **Hib PRP**: Non-inferiority met using pre-determined criteria. **GMCs and GMRs:** **Hib PRP:** GMR met pre-determined non-inferiority criteria and significantly favours Vaxelis (23.25, 95% CI 15.11 to 35.78). **Tetanus, pertussis PT:** GMCs significantly higher in Vaxelis group. **Diphtheria, pertussis FHA:** GMCs significantly lower in Vaxelis group. **Hepatitis B, pertussis PRN**: No statistical difference in GMCs between Vaxelis and Infanrix hexa group.				⨁⨁⨁⨁ High	CRITICAL
Immunogenicity at 13 months after 3 primary doses and 1 dose of Hib(PRP-TT)/MenC given at 12 months of age (follow-up: 1 month; assessed with: percentage participants with antibody titres above cutoff values AND geometric mean concentrations)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	Oxford (Unpublished)[2]: Selected endpoints **Percentage participants achieving antibody titres above set cutoff values:** **Diphtheria, tetanus, Hib PRP, hepatitis B:** No statistical difference between Vaxelis and Infanrix hexa groups. **GMCs and GMRs:** **Hepatitis B, pertussis FHA:** GMCs significantly lower in Vaxelis group. **Hib PRP:** GMCs significantly higher in Vaxelis group. **Pertussis PT / PRN:** No statistical difference between Vaxelis and Infanrix hexa groups.				⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis)	DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa)	Relative (95% CI)	Absolute (95% CI)		
Immunogenicity at 13 months after 3 primary doses and 1 booster dose (follow-up: 1 month; assessed with: percentage participants with antibody titres above cutoff values AND geometric mean concentrations)												
1	randomised trials	not serious	not serious	not serious	not serious	none	Vesikari (2017)[1]: Selected endpoints **Percentage participants achieving antibody titres above set cutoff values:** **Hib PRP:** No statistical difference between Vaxelis and Infanrix hexa groups. **Hepatitis B, pertussis PT / FHA / PRN:** met pre-determined non-inferiority criteria with no statistical difference between Vaxelis and Infanrix hexa groups. **GMCs and GMRs:** **Hib PRP, pertussis FHA:** GMCs significantly lower in Vaxelis group. **Pertussis PT:** GMCs significantly higher in Vaxelis group. **Hepatitis B, pertussis PRN:** No statistical difference between Vaxelis and Infanrix hexa groups.		⨁⨁⨁⨁ High		CRITICAL
Immunogenicity at 13 months after 2 primary doses and 1 booster dose (follow-up: 1 month; assessed with: percentage participants with antibody titres above cutoff values)												
1	randomised trials	not serious	not serious	not serious	not serious	none	Silfverdal (2016)[3]: Selected endpoints **Percentage participants achieving antibody titres above set cutoff values:** **All 10 vaccine antigens:** Met pre-determined non-inferiority criteria with no statistical difference between Vaxelis and Infanrix hexa groups.		⨁⨁⨁⨁ High		CRITICAL
Serious Adverse Events (follow-up: dose 1 to 1 month after final dose; assessed with: symptom diaries)												
3	randomised trials	not serious	not serious	not serious[b]	not serious	none	Silfverdal (2016)[3]: Difference in percentage participants reporting serious AEs after any dose Vaxelis and Infanrix hexa (ref) **All:** -0.3% **Vaccine-related:** -0.2% Vesikari (2017)[1]: Difference in percentage participants reporting serious AEs after any dose Vaxelis (ref) and Infanrix hexa **All:** 0.6% (-1.2% to 2.5%) **Vaccine-related:** 0.2% (-0.6% to 1.0%) Oxford (Unpublished)[2]: Participants reporting serious AEs after any dose Vaxelis (ref) and Infanrix hexa **All:** 2.2% **Vaccine-related:** 1 participant in the Infanrix hexa group		⨁⨁⨁⨁ High		CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis)	DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa)	Relative (95% CI)	Absolute (95% CI)		
IMPORTANT OUTCOMES												
Systemic Adverse Events (follow-up: range 5 days to 15 days; assessed with: symptom diaries)												
3	randomised trials	not serious	not serious	serious[b]	not serious	none	Silfverdal (2016)[3]: Difference in percentage participants with solicited and unsolicited systemic AEs after any dose Vaxelis and Infanrix hexa (ref) **All:** 0.14% **Vaccine-related:** 0.75% Statistically significant differences in percentage of participants with solicited pyrexia and somnolence (see "Fever" and "Adverse Events of Special Interest" outcomes) Vesikari (2017)[1]: Difference in percentage participants with solicited and unsolicited systemic AEs after any dose Vaxelis and Infanrix hexa (ref) **All:** -1.0% (-2.4% to 0.3%) **Vaccine-related:** -0.9% (-3.2% to 1.3%) Oxford (Unpublished)[2]: Difference in percentage participants with solicited systemic AEs after each primary dose of Vaxelis and Infanrix hexa (ref) **All:** -5.4% to 4.7% **Severe:** 0.1% to 3.8%				⨁⨁⨁◯ Moderate	IMPORTANT
Local Adverse Events (follow-up: range 5 days to 15 days; assessed with: symptom diaries)												
2	randomised trials	not serious	not serious	serious[b]	not serious	none	Silfverdal (2016)[3]: Difference in percentage participants with solicited and unsolicited local AEs after any dose (including toddler booster dose) Vaxelis and Infanrix hexa (ref) **All:** 2.65% Vesikari (2017)[1]: Difference in percentage participants with solicited and local systemic AEs after any dose (including toddler booster dose) Vaxelis and Infanrix hexa (ref) **All:** 1.09%				⨁⨁⨁◯ Moderate	IMPORTANT
Fever (follow-up: range 5 days to 15 days; assessed with: daily temperature measurements AND symptom diaries)												
3	randomised trials	not serious	not serious	serious[b]	not serious	none	Silfverdal (2016)[3]: Difference in percentage participants after any dose (including toddler booster dose) Vaxelis and Infanrix hexa (ref) for: Measured temperature **>38.0C** on day 1-5: 7.02% Measured temperature **≥39.5C (severe)** on day 1-5: 1.6% (-0.5% to 3.7%) **Solicited pyrexia:** 6.4% (1.5% to 11.3%) Vesikari (2017)[1]: Difference in percentage participants after any dose (including toddler booster dose) Vaxelis and Infanrix hexa (ref) for: Measured temperature **>38.0C** on day 1-5: -1.19% Measured temperature **≥39.5C (severe)** on day 1-5: -0.8% (-3.0% to 1.3%) **Solicited pyrexia**: -1.7% (-6.7% to 3.4%) Oxford (Unpublished)[2]: Difference in percentage participants after each primary dose Vaxelis and Infanrix hexa (ref) for: Measured temperature **>37.5C** on day 0-5: -3.1% to 0.4% Measured temperature classified as **severe fever** on day 0-5: -1.1% to 0%				⨁⨁⨁◯ Moderate	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DT5aP-HBV-IPV-Hib(PRP-OMP) (Vaxelis)	DT3aP-HBV-IPV-Hib(PRP-TT) (Infanrix hexa)	Relative (95% CI)	Absolute (95% CI)		
Adverse Event of Special Interest: Somnolence / Drowsiness (follow-up: range 5 days to 15 days; assessed with: symptom diaries)												
3	randomised trials	not serious	not serious	serious[b]	not serious	none	Silfverdal (2016)[3]: Difference in percentage participants with solicited somnolence after any dose (including toddler booster dose) Vaxelis and Infanrix hexa (ref): 5.8% (1.78% to 9.8%) Vesikari (2017)[1]: Difference in percentage participants with solicited somnolence after any dose (including toddler booster dose) Vaxelis and Infanrix hexa (ref): -3.2% (-7.8% to 1.4%) Oxford (Unpublished)[2]: Difference in percentage participants with solicited drowsiness after each primary dose Vaxelis and Infanrix hexa (ref): -5.7% to 9.7%				⨁⨁⨁◯ Moderate	IMPORTANT

AE: adverse event; **CI:** confidence interval; **GMC:** geometric mean concentration; **GMR:** geometric mean ratio; **ref:** reference group

Explanations

a. The Oxford study is a small study with 194 enrolled participants in total.
b. Both the Silfverdal and Vesikari studies pool safety outcome data between the 3 infant doses and the toddler booster dose.

Evidence to Decision Framework: Individual perspective

Patients: 6 months to 10 years

Intervention: DT5aP-HBV-IPV-Hib(PRP-OMP) vaccine (Vaxelis) for primary vaccination

Comparison: DT3aP-HBV-IPV-Hib(PRP-TT) vaccine (Infanrix hexa) for primary vaccination

Main outcomes:

- Immunogenicity at 5 months of age after 3 primary doses
- Immunogenicity at 13 months of age after 3 primary doses and 1 dose of Hib(PRP-TT)/MenC given at 12 months of age
- Immunogenicity at 13 months of age after 3 primary doses and 1 booster dose
- Immunogenicity at 13 months of age after 2 primary doses and 1 booster dose
- Serious adverse events (SAE)
- Systemic adverse events
- Local adverse events
- Fever
- Adverse events of special interest (AESI)

Setting: Global middle-high-income settings (e.g. European Union, UK, Australia)

Perspective: Individual

Background

Vaxelis is expected to be introduced in Australia in 2022. It is directed against the same six conditions as Infanrix hexa: diphtheria, tetanus, pertussis, hepatitis B, polio and *Haemophilus influenzae* type b (Hib). It is approved for use under the National Immunisation Program as a primary vaccine course given at 2, 4 and 6 months of age, and for catch-up vaccination up to 10 years of age.

ASSESSMENT

Problem

Is the problem a priority?

Don't know	Varies	No	Probably no	Probably yes	Yes
					■

- The six conditions targeted by Vaxelis have the potential to cause substantial morbidity and mortality if adequate individual and population vaccine coverage are not maintained.

Desirable effects

How substantial are the desirable anticipated effects?

Don't know	Varies	Trivial	Small	Moderate	Large
		■			

- Vaxelis demonstrates little or no difference in its immunogenicity against the six targeted conditions compared to Infanrix hexa.[1-3]
- Two additional large randomised trials comparing Vaxelis to the DT5aP-IPV-Hib(PRP-TT) vaccine (Pentacel) and recombinant hepatitis B vaccine (HB-Vax-II) in infants and toddlers in the US, demonstrate little or no difference in immunogenicity.[4,5]

- A sub-analysis of a small number of American Indian children, within one of the additional US trials above, demonstrated higher immunogenicity of Vaxelis against *Haemophilus influenzae* type b compared to Pentacel. These results may have some relevance to the Australian setting.[5]
- Two studies followed children who had originally participated in the Vesikari or Silfverdal studies.[6,7] They demonstrated little or no difference in immune response to hepatitis B and pertussis antigens between children 4 to 5 years of age who had received 3 infant doses of Vaxelis or Infanrix hexa, and 93.6% to 98.9% seroconversion to a challenge dose of hepatitis B vaccine in children 8 to 9 years of age who had originally received infant and toddler doses of Vaxelis.

Undesirable effects

How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Vaxelis demonstrates little or no difference in the frequency or severity of adverse events compared to Infanrix hexa.[1-3]
- Studies comparing Vaxelis to Pentacel and H-B-Vax II showed a higher frequency of pyrexia and mild to moderate measured fever in the Vaxelis groups.[4,5]
- Evidence on the effect of Vaxelis on immunogenicity to antigens in co-administered vaccines, compared to that of Infanrix hexa, is limited, and suggests little to no difference between the two vaccines.[2,3,5]

Certainty of evidence

What is the overall certainty of the evidence of effects?

No included studies	Very low	Low	Moderate	High

- Evidence on the immunogenicity and safety of Vaxelis compared to Infanrix hexa was from three randomised controlled trials where the risk of bias was assessed to be low.
- There is little evidence to date on the effects of Vaxelis on immunogenicity of co-administered vaccines.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Important uncertainty	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability

- Unlikely to be important uncertainty in how people value protection against the six targeted conditions using either Vaxelis or Infanrix hexa.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Don't know	Varies	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention

• The overall balance of desirable and undesirable effects of Vaxelis are comparable to those of Infanrix hexa.					
Acceptability Is the intervention acceptable to key stakeholders?					
Don't know	Varies	No	Probably no	Probably yes	Yes
• Vaxelis may be easier to administer compared to Infanrix hexa as: it is fully liquid and does not require reconstitution of the Hib component, it is presented as a pre-filled Luer-lock syringe, it has a longer refrigerated shelf life, and longer stability at room temperature. A time and motion study showed preference among vaccinators for fully liquid hexavalent infant.[8]					
Feasibility Is the intervention feasible to implement?					
Don't know	Varies	No	Probably no	Probably yes	Yes
• Systems and processes for vaccine delivery are already in use. However, there is currently no evidence to support the interchangeability of Vaxelis and Infanrix hexa in the primary infant schedule, which may limit its implementation.					

References

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