

# 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	<ul> <li>Critical</li> <li>Immunogenicity at 5 months of age following a 3-dose primary course</li> <li>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</li> <li>Immunogenicity at 13 months of age following a 3-dose primary course and 1 booster dose at 12 months</li> <li>Immunogenicity at 13 months of age following a 2-dose primary course and 1 booster dose at 12 months</li> <li>Serious adverse events</li> </ul>							
	Important <ul> <li>Systemic adverse events</li> <li>Local adverse events</li> <li>Fever</li> <li>Other AESI (Systemic and Local)</li> </ul>							



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.

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

#### Table 3: Rationale for PICO and inclusion criteria



Comparator	The intended use of Vaxelis is at the same time points and for the same population as Infanrix hexa.
DT3aP-HBV-IPV- Hib(PRP-TT) (Infanrix hexa) as primary vaccination course	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

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



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



34exp Treatment Outcome/ (1206245)34exp drug efficacy/ (966181)#38McSH descriptor: [Safety-Based Drug35efficack.tw. (1474564)35efficacks.tw. (1474564)#39McSH descriptor: [Drug-Related Side Effects and37exp Safety/ (87633)37exp drug safety/ (503749)Adverse Reactions] explode all trees387938exp Safety-Based Drug Withdrawals/38exp postmarketing surveillance/#30McSH descriptor: [Drug-Related Side Effects and40Adverse Reactions"/ (128239)(26605)#40exp adverse drug reaction/ (590473)#41McSH descriptor: [Adverse Drug Reaction40exp Drug Evaluation/ (42040)(664884)(664884)#42McSH descriptor: [Adverse Drug Reaction41exp Drug Evaluation/ (42040)(664884)(adverse adj2 (effects or events)).tw.43((post marketing or post-marketing or post-licensure or postlicensure or post-marketing or post-marketing or post-marketing OR post-licensure OR#45(fraise% or fise%) adj347((raise% or rise%) adj3temperature%).tw. (11158)#46McSH descriptor: [Fover] explode all trees 220846((raise% or rise%) adj3temperature%).tw. (10306)8 or 39 or 40 or 41 or 42 or 43 or 44 or 45%43470p rest inse%) adj3sor or for 25 or 26 or 27 or								
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$ \begin{array}{c} 37  \exp Safety (87633) \\ 38  \exp Safety - Based Drug Withdrawals/ \\ (414) \\ 39  \exp \ Drug - Related Side Effects and \\ Adverse Reactions'' (128239) \\ 40  \exp \ Drug - Related Side Effects and \\ Adverse Reactions'' (128239) \\ 40  \exp \ Drug - Related Side Effects and \\ Adverse Reactions'' (128239) \\ 40  \exp \ Drug - Related Side Effects and \\ Adverse Reactions'' (128239) \\ 40  \exp \ Drug - Related Side Effects and \\ Adverse Reactions'' (128239) \\ 40  \exp \ Drug - Related Side Effects and \\ Adverse Reactions'' (128239) \\ 41  \exp \ Drug - Related Side Effects and \\ Adverse Reactions'' (128239) \\ 41  \exp \ Drug - Related Side Effects and \\ Adverse Reactions'' (128239) \\ 41  \exp \ Drug - Related Side Effects and \\ Adverse Reactions'' (128239) \\ 42  \exp \ Drug - Related Side Effects and \\ Adverse Reaction' (590473) \\ 41  (adverse adj2 (effects' or events')).tw. \\ 42  exp \ Adverse Drug Reaction Reporting \\ Systems (8558) \\ 43  (adverse adj2 (effects' or events')).tw. \\ (424595) \\ 44  (safe or safety or aefi or aesi).tw. \\ (1428477) \\ 43  ((atsee's or safety or aefi or aesi).tw. \\ (1428477) \\ 43  ((atsee's or safety or aefi or aesi).tw. \\ (1428477) \\ 44  (safe or safety or aefi or aesi).tw. \\ (1428477) \\ 45  ((post marketing or post-marketing or post-licensure or post-lic$	35 efficac\$.tw. (1016230)	35 efficac\$.tw. (1474564)	Withdrawals] explode all trees 11					
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(414)(38094)Postmarketing] explode all trees21539expmost actions"/ (128239)39expdrug surveillance program/#41McSH descriptor: [Drug Evaluation] explode all40expProduct Surveillance,40exp adverse drug reaction / (590473)#42McSH descriptor: [Adverse Drug Reaction41expDrug Evaluation / (42040)42(safe or safety or aefi or aesi).tw.(664884)#43(adverse NEAR/2 (effect* OR event*)):ti, ab,kw22expAdverse adj2 (effect\$ or event\$)).tw.(1282477)#44(safe OR safety OR aefi OR aesi):ti, ab,kw44(safe or safety or aefi or aesi).tw.(1428477)#3((post marketing or post-incensure or post-44(safe or safety or aefi or aesi).tw.(icruses or fiver\$).tw. (5272)monitor\$)).tw. (5272)9ostmarketing or post licensure or post-iccruser or postlicensure or post-licensure or post-licensure or post-#46McSH descriptor: [Fever] explode all trees10(queres adj2 (effect\$ or event\$)).tw.45((post marketing or post licensure or post-#44(safe OR safety OR aefi OR aesi):ti, ab,kw2945((post marketing or post-licensure or post-iccnsure or postlicensure) adj2monitor\$).tw. (273164)#4646(craise\$ or rise\$) adj3temperature\$).tw. (11158)#47(pyrexia\$ OR fever*):ti, ab,kw2259148((raise\$ or rise\$) adj3as or 39 or 40 or 41 or 42 or 43 or 44 or 45McSH descriptor: [Fever] explode all trees220847(pyrexia\$ or fiver\$).tw. (10306)	37 exp Safety/ (87633)		Adverse Reactions] explode all trees 3879					
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Adverse Reactions"/ (128239)(26605)trees575140exp Product Surveillance,40exp adverse drug reaction/ (590473)#42McSH descriptor: [Adverse Drug Reaction41exp Drug Evaluation/ (42040)(264884)(2(safe or safety or aefi or aesi).tw.(1428477)43(adverse adj2 (effect\$ or event\$)).tw.(42 (safe or safety or aefi or aesi).tw.(1428477)#43((post marketing or post-marketing or post-mark	(414)	(38094)	Postmarketing] explode all trees 215					
40exp Product Surveillance, Postmarketing/ (17670)40exp adverse drug reaction/ (590473) 41#42MeSH descriptor: [Adverse Drug Reaction Reporting Systems] explode all trees9541exp Drug Evaluation/ (42040)41(adverse adj2 (effect\$ or event\$)).tw. (664884)(664884)#43(adverse NEAR/2 (effect* OR event*)):ti, ab,kw 27876343(adverse adj2 (effect\$ or event\$)).tw. (424595)(42 (safe or safety or aefi or aesi).tw. (1428477)(1428477)#44(safe OR safety OR aefi OR aesi):ti, ab,kw 30463044(safe or safety or aefi or aesi).tw. (949883)((post marketing or post-marketing or postmarketing or post licensure or postlicensure) adj2 (surveillance or monitor\$)).tw. (3456)((raise\$ or fise\$) adj3 (traise\$ or fise\$) adj3#45((post marketing OR post-marketing OR postmarketing OR post-licensure OR postmarketing or post licensure or post-licensure or post-licensure or postlicensure) adj2 (surveillance or monitor\$)).tw. (3456)#4(raise\$ or rise\$) adj3 temperature\$).tw. (10306)#4724 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)#4823 and 47 (16)#44OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 900363	39 exp "Drug-Related Side Effects and	39 exp drug surveillance program/	#41 MeSH descriptor: [Drug Evaluation] explode all					
Postmarketing/ (17670)41 (adverse adj2 (effect\$ or event\$)).tw.Reporting Systems] explode all trees9541 exp Drug Evaluation/ (42040)42 exp Adverse Drug Reaction Reporting42 (safe or safety or aefi or aesi).tw.(664884)27876343 (adverse adj2 (effect\$ or event\$)).tw.42 (safe or safety or aefi or aesi).tw.(1428477)#44 (safe OR safety OR aefi OR aesi):ti, ab,kw44 (safe or safety or aefi or aesi).tw.(1428477)304630#45 ((post marketing OR post-marketing OR post-marketing OR post-marketing or post licensure or post-licensure or postlicensure) adj2#46 MeSH descriptor: [Fever] explode all trees(949883)45 ((post marketing or post licensure or post-licensure or post-licensure or postlicensure) adj2(surveillance or monitor\$)).tw. (5272)#46 MeSH descriptor: [Fever] explode all trees45 ((post marketing or post licensure or post-licensure or postlicensure) adj2(surveillance or monitor\$)).tw. (11158)#46 MeSH descriptor: [Fever] explode all trees46 exp Fever/ (46597)47 24 or 25 or 26 or 27 or 28 or 29 or 30or 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#48 ((raise* OR rise*) NEAR/348 ((raise\$ or rise\$) adj3remperature\$).tw. (10306)80 or 99 or 40 or 41 or 42 or 43 or 44 or 45#49 #24 OR #25 OR #26 OR #27 OR #28 OR #2949 24 or 25 or 26 or 27 or 28 or 29 or 30ra 66 (6706914)8 23 and 47 (16)8 23 and 47 (16)49 24 or 35 or 33 or 34 or 35 or 36 or 37 or80 R#34 OR #44 OR #45 OR #46 OR #47 OR #4840 OR #44 OR #45 OR #46 OR #47 OR #4841 (adverse adj2 (effect\$ or event\$)).tw.48 2 3 and 47 (16)	Adverse Reactions"/ (128239)	(26605)	trees 5751					
41exp Drug Evaluation/ (42040)42exp Adverse Drug Reaction ReportingSystems/ (8558)4243(adverse adj2 (effect\$ or event\$)).tw.44(safe or safety or aefi or aesi).tw.(424595)4344(safe or safety or aefi or aesi).tw.(949883)4545((post marketing or post-marketing or postmarketing or post licensure or post- licensure or postlicensure) adj245((post marketing or post-marketing or postmarketing or post licensure or post- licensure or postlicensure) adj2(surveillance or monitor\$)).tw. (3456)4646exp Fever/ (46597)47(pyrexia\$ or fever\$).tw. (11158)46exp Fever/ (46597)48((raise\$ or rise\$) adj3 temperature\$).tw. (10306)4924 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 or4924 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 or4924 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 or4924 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 or4924 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 or4924 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 or4082 and 47 (16)	40 exp Product Surveillance,	40 exp adverse drug reaction/ (590473)	#42 MeSH descriptor: [Adverse Drug Reaction					
42exp Adverse Drug Reaction Reporting Systems/ (8558)42(safe or safety or aefi or aesi).tw. (1428477)27876343(adverse adj2 (effect\$ or event\$)).tw. (424595)43((post marketing or post-licensure or post- licensure or post- (surveillance or monitor\$)).tw. (3456)42(safe or safety or aefi or aesi).tw. (1428477)43((post marketing or post-marketing OR postmarketing OR post-marketing OR postmarketing OR post-licensure OR postmarketing or post-licensure or post- licensure or postlicensure or post- licensure or postlicensure adj2 (surveillance or monitor\$)).tw. (3456)44exp fever/ (293659) 45#44(safe OR safety OR aefi OR aesi):ti,ab,kw 30463046((post marketing or post-marketing or postmarketing or post-marketing or post-licensure or post- licensure or postlicensure or post- licensure or postlicensure or post- licensure or postlicensure or post- licensure or postlicensure) adj2 (surveillance or monitor\$)).tw. (1158)#46MeSH descriptor: [Fever] explode all trees2208 #4747(pyrexia\$ or fever\$).tw. (199644) or 31 or 32 or 33 or 34 or 35 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 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or88 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 (6706914)#48(raise\$ OR #31 OR #32 OR #34 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 900363	Postmarketing/ (17670)	41 (adverse adj2 (effect\$ or event\$)).tw.	Reporting Systems] explode all trees 95					
Systems/ (8558)(1428477)#44 (safe OR safety OR aefi OR aesi):ti,ab,kw 30463043 (dverse adj2 (effect\$ or event\$)).tw. (424595)43 ((post marketing or post-marketing or postmarketing or post licensure or post- licensure or postlicensure) adj2 (surveillance or monitor\$)).tw. (5272)#44 (safe OR safety OR aefi OR aesi):ti,ab,kw 30463044 (safe or safety or aefi or aesi).tw. (949883)(gurveillance or monitor\$)).tw. (5272)#44 (exp fever/ (293659))45 ((post marketing or post licensure or post- licensure or postlicensure) adj2 (surveillance or monitor\$)).tw. (3456)44 (exp fever/ (293659))46 (raise\$ or rise\$) adj3 (surveillance or monitor\$)).tw. (3456)45 (pyrexia\$ or fever\$).tw. (273164) 46 ((raise\$ or rise\$) adj3 temperature\$).tw. (11158)#46 MeSH descriptor: [Fever] explode all trees2208 #47 (pyrexia* OR fever*):ti,ab,kw 22591 #48 ((raise* or rise\$) adj3 temperature\$).tw. (10306)47 (pyrexia\$ or fever\$).tw. (10306)73 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 44 or 46 (6706914)78 23 and 47 (16)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 or78 and 47 (16)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 or78 and 47 (16)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 or78 and 47 (16)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 or78 and 47 (16)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 or78 and 47 (16)40 24 or 32 or 33 or 34 or 35 or 36 or 37 or78 and 47 (16	41 exp Drug Evaluation/ (42040)	(664884)	#43 (adverse NEAR/2 (effect* OR event*)):ti,ab,kw					
Systems/ (8558)(1428477)#44 (safe OR safety OR aefi OR aesi):ti,ab,kw 30463043 (adverse adj2 (effect\$ or event\$)).tw. (424595)43 ((post marketing or post-marketing or postmarketing or post-licensure or post- licensure or postlicensure) adj2 (surveillance or monitor\$)).tw. (5272)#44 (safe OR safety OR aefi OR aesi):ti,ab,kw 30463045 ((post marketing or post-marketing or postmarketing or post-licensure or post- licensure or postlicensure) adj2 (surveillance or monitor\$)).tw. (3456)44 exp fever/ (293659) 45 (pyrexia\$ or fiever\$).tw. (273164) 46 ((raise\$ or rise\$) adj3 temperature\$).tw. (199644)#44 (safe OR safety OR aefi OR aesi):ti,ab,kw 30463046 exp Fever/ (46597)45 (pyrexia\$ or fiever\$).tw. (273164) 46 ((raise\$ or rise\$) adj3 temperature\$).tw. (1158)#46 (raise\$ or Rise*) NEAR/3 temperature\$).tw. (199644)48 ((raise\$ or rise\$) adj3 temperature\$).tw. (10306)47 24 or 25 or 26 or 27 or 28 or 29 or 30 or 46 (6706914)30 at 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 (raise* OR #30 OR #31 OR #32 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	42 exp Adverse Drug Reaction Reporting	42 (safe or safety or aefi or aesi).tw.	278763					
(424595)postmarketing or post licensure or post- licensure or post-licensure or post- licensure or post-	Systems/ (8558)	(1428477)	#44 (safe OR safety OR aefi OR aesi):ti,ab,kw					
(424595)postmarketing or post licensure or post- licensure or postlicensure) adj2 (surveillance or monitor\$)).tw. (5272)#45 ((post marketing OR post-marketing OR postmarketing OR post-licensure OR postmarketing or post licensure or post- licensure or post- licensure or post- licensure or post- licensure or post-licensure) adj2 (surveillance or monitor\$)).tw. (3456)#46 exp Fever/ (293659)#46 ((raise\$ or rise\$) adj3 temperature\$).tw. (273164) 46 ((raise\$ or rise\$) adj3 temperature\$).tw. (11158)#46 MeSH descriptor: [Fever] explode all trees2208 #47 (pyrexia\$ or fever\$).tw. (1158)46 exp Fever/ (46597)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 temperature\$).tw. (10306)47 24 or 25 or 26 or 27 or 28 or 29 or 30 or 46 (6706914)#48 23 and 47 (16)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 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #44 OR #45 OR #46 OR #47 OR #48 900363	43 (adverse adj2 (effect\$ or event\$)).tw.	43 ((post marketing or post-marketing or	304630					
	(424595)		#45 ((post marketing OR post-marketing OR					
45 ((post marketing or post-marketing or postmarketing or post licensure or post- licensure or postlicensure) adj2 $44$ exp fever/ (293659)monitor*)):ti,ab,kw $1279$ $45$ (pyrexia\$ or fever\$).tw. (273164) $45$ (pyrexia\$ or fever\$).tw. (273164) $46$ ((raise\$ or rise\$) adj3#47 (pyrexia* OR fever*):ti,ab,kw $22591$ $46$ exp Fever/ (46597) $47$ 24 or 25 or 26 or 27 or 28 or 29 or 30 $47$ (pyrexia\$ or fever\$).tw. (199644) $47$ 24 or 25 or 26 or 27 or 28 or 29 or 30 $73$ or 31 or 32 or 33 or 40 or 41 or 42 or 43 or 44 or 45 $49$ 24 or 25 or 26 or 27 or 28 or 29 or 30 $48$ 23 and 47 (16) $48$ 23 and 47 (16) $48$ 23 and 47 (16) $49$ 24 or 25 or 33 or 34 or 35 or 36 or 37 or or 31 or 32 or 33 or 34 or 35 or 36 or 37 or $48$ 23 and 47 (16) $48$ 23 and 47 (16) $48$ 23 and 47 (16)	44 (safe or safety or aefi or aesi).tw.	licensure or postlicensure) adj2	postmarketing OR post licensure OR post-licensure OR					
postmarketing or post licensure or post- licensure or postlicensure) adj2 (surveillance or monitor\$)).tw. (3456)45(pyrexia\$ or fever\$).tw. (273164)#46MeSH descriptor: [Fever] explode all trees220846((raise\$ or rise\$) adj3 temperature\$).tw. (11158)46((raise\$ or rise\$) adj3 temperature\$).tw. (11158)#46MeSH descriptor: [Fever] explode all trees220847(pyrexia\$ or fever\$).tw. (3456)4724 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#46MeSH descriptor: [Fever] explode all trees220848((raise\$ or rise\$) adj3 temperature\$).tw. (10306)or 31 or 32 or 33 or 34 or 35 or 36 or 37 or or 46 (6706914)#470R #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	(949883)	(surveillance or monitor\$)).tw. (5272)	postlicensure) NEAR/2 (surveillance OR					
licensure or postlicensure) adj2       46 ((raise\$ or rise\$) adj3       #47 (pyrexia* OR fever*):ti,ab,kw 22591         (surveillance or monitor\$)).tw. (3456)       46 ((raise\$ or rise\$) adj3       #47 (pyrexia* OR fever*):ti,ab,kw 22591         46 exp Fever/ (46597)       47 24 or 25 or 26 or 27 or 28 or 29 or 30       #48 ((raise* OR rise*) NEAR/3         47 (pyrexia\$ or fever\$).tw. (199644)       47 24 or 25 or 26 or 27 or 28 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or       #49 #24 OR #25 OR #26 OR #27 OR #28 OR #29         48 ((raise\$ or rise\$) adj3       38 or 39 or 40 or 41 or 42 or 43 or 44 or 45       OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR         49 24 or 25 or 26 or 27 or 28 or 29 or 30       or 46 (6706914)       #8 23 and 47 (16)       #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	45 ((post marketing or post-marketing or	44 exp fever/ (293659)	monitor*)):ti,ab,kw 1279					
licensure or postlicensure) adj2       46 ((raise\$ or rise\$) adj3       #47 (pyrexia* OR fever*):ti,ab,kw 22591         (surveillance or monitor\$)).tw. (3456)       temperature\$).tw. (11158)       #48 ((raise* OR rise*) NEAR/3         46 exp Fever/ (46597)       47 24 or 25 or 26 or 27 or 28 or 29 or 30       temperature\$).tw. (199644)         47 (pyrexia\$ or fever\$).tw. (199644)       or 31 or 32 or 33 or 34 or 35 or 36 or 37 or       #49 #24 OR #25 OR #26 OR #27 OR #28 OR #29         48 ((raise\$ or rise\$) adj3       38 or 39 or 40 or 41 or 42 or 43 or 44 or 45       OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR         49 24 or 25 or 26 or 27 or 28 or 29 or 30       or 46 (6706914)       #8 23 and 47 (16)         48 23 and 47 (16)       OR #43 OR #44 OR #45 OR #46 OR #47 OR #48         900363	postmarketing or post licensure or post-	45 (pyrexia\$ or fever\$).tw. (273164)	#46 MeSH descriptor: [Fever] explode all trees2208					
46       exp Fever/ (46597)       47       24 or 25 or 26 or 27 or 28 or 29 or 30       temperature*):ti,ab,kw       380         47       (pyrexia\$ or fever\$).tw. (199644)       or 31 or 32 or 33 or 34 or 35 or 36 or 37 or       temperature*):ti,ab,kw       380         48       ((raise\$ or rise\$) adj3       38 or 39 or 40 or 41 or 42 or 43 or 44 or 45       OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR         49       24 or 25 or 26 or 27 or 28 or 29 or 30       or 46 (6706914)       #8       23 and 47 (16)         48       23 and 47 (16)       0R #43 OR #44 OR #45 OR #46 OR #47 OR #48       900363		46 ((raise\$ or rise\$) adj3						
47       (pyrexia\$ or fever\$).tw. (199644)       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       #49       #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR 0R #31 OR #32 OR #33 OR #34 OR #35 OR 0R #31 OR #32 OR #33 OR #40 OR #41 OR #42         48       ((raise\$ or rise\$) adj3       or 46 (6706914)       0r 46 (6706914)       0R #30 OR #31 OR #32 OR #38 OR #39 OR #40 OR #41 OR #42       0R #43 OR #44 OR #45 OR #46 OR #47 OR #48         49       24 or 25 or 26 or 27 or 28 or 29 or 30       48       23 and 47 (16)       0R #43 OR #44 OR #45 OR #46 OR #47 OR #48         000363       900363       900363       000363       000363       000363	(surveillance or monitor\$)).tw. (3456)	temperature\$).tw. (11158)	#48 ((raise* OR rise*) NEAR/3					
47       (pyrexia\$ or fever\$).tw. (199644)       or 31 or 32 or 33 or 34 or 35 or 36 or 37 or       #49       #24 OR #25 OR #26 OR #27 OR #28 OR #29         48       ((raise\$ or rise\$) adj3       38 or 39 or 40 or 41 or 42 or 43 or 44 or 45       OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR         49       24 or 25 or 26 or 27 or 28 or 29 or 30       or 46 (6706914)       #4       23 and 47 (16)         or 31 or 32 or 33 or 34 or 35 or 36 or 37 or       48       23 and 47 (16)       OR #43 OR #44 OR #45 OR #46 OR #47 OR #48			temperature*):ti,ab,kw 380					
48       ((raise\$ or rise\$) adj3       38 or 39 or 40 or 41 or 42 or 43 or 44 or 45       OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR         temperature\$).tw. (10306)       or 46 (6706914)       #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42         49       24 or 25 or 26 or 27 or 28 or 29 or 30       48       23 and 47 (16)         or 31 or 32 or 33 or 34 or 35 or 36 or 37 or       000000000000000000000000000000000000	47 (pyrexia\$ or fever\$).tw. (199644)	or 31 or 32 or 33 or 34 or 35 or 36 or 37 or						
temperature\$).tw. (10306)       or 46 (6706914)       #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42         49       24 or 25 or 26 or 27 or 28 or 29 or 30       48       23 and 47 (16)         or 31 or 32 or 33 or 34 or 35 or 36 or 37 or       48       23 and 47 (16)		38 or 39 or 40 or 41 or 42 or 43 or 44 or 45	OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR					
49       24 or 25 or 26 or 27 or 28 or 29 or 30       48       23 and 47 (16)       OR #43 OR #44 OR #45 OR #46 OR #47 OR #48         or 31 or 32 or 33 or 34 or 35 or 36 or 37 or       900363       900363		or 46 (6706914)	#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42					
		48 23 and 47 (16)	OR #43 OR #44 OR #45 OR #46 OR #47 OR #48					
	or 31 or 32 or 33 or 34 or 35 or 36 or 37 or		900363					
38 or 39 or 40 or 41 or 42 or 43 or 44 or 45   #50 #23 AND #49 5	38 or 39 or 40 or 41 or 42 or 43 or 44 or 45		#50 #23 AND #49 5					
or 46 or 47 or 48 (5336887)								
50 23 and 49 (9)								



## Appendix B: Risk of Bias: ROB 2.0

Intention-to-														
treat	<u>Unique ID</u>	Study ID	<b>Experimental</b>	<u>Comparator</u>	Outcome	<u>Weight</u>	<u>D1</u>	<u>D2</u>	<u>D3</u>	<u>D4</u>	<u>D5</u>	Overall	_	
	Vaxelis_IO1_0	00 Vesikari	Vaxelis	Infanrix hexa	Immunogenicity 1 5 months 3 doses	1	•	•	•	•	+	•	•	Low risk
	Vaxelis_IO1_6	5ir Snape	Vaxelis	Infanrix hexa	Immunogenicity 1 5 months 3 doses	1	•	•	+	+	+	•	!	Some concerns
	Vaxelis_IO2_0	00 Vesikari	Vaxelis	Infanrix hexa	Immunogenicity 2 13 months 3 plus 1 doses	1	•	•	+	+	+	•	•	High risk
	Vaxelis_IO2_6	5ir Snape	Vaxelis	Infanrix hexa	Immunogenicity 2 13 months 3 plus 1 doses	1	•	•	•	+	+	•		
	Vaxelis_IO3_0	00 Silfverdal	Vaxelis	Infanrix hexa	Immunogenicity 3 13 months 2 plus 1 doses	1	+	•	+	+	+	•	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	<u>Comparator</u>	Outcome	Weight	<u>D1</u>	<u>D2</u>	D3	<u>D4</u>	<u>D5</u>	Overall		
	Vaxelis_S1_008	Silfverdal	Vaxelis	Infanrix hexa	Safety 1 SAEs	1	•	•	•	•	•	•	•	Low risk
	Vaxelis_S1_007	Vesikari	Vaxelis	Infanrix hexa	Safety 1 SAEs	1	•	•	•	•	•	•	!	Some concerns
	Vaxelis_S1_6in1	Snape	Vaxelis	Infanrix hexa	Safety 1 SAEs	1	•	•	•	•	!	•	•	High risk
	Vaxelis_S2_008	Silfverdal	Vaxelis	Infanrix hexa	Safety 2 Systemic AEs	1	•	•	•	•	•	•		
	Vaxelis_S2_007	Vesikari	Vaxelis	Infanrix hexa	Safety 2 Systemic AEs	1	•	•	•	•	•	•	D1	Randomisation process
	Vaxelis_S2_6in1	Snape	Vaxelis	Infanrix hexa	Safety 2 Systemic AEs	1	•	•	•	!	•	!	D2	Deviations from the intended interventions
	Vaxelis_S3_008	Silfverdal	Vaxelis	Infanrix hexa	Safety 3 Local AEs	1	•	•	•	•	•	•	D3	Missing outcome data
	Vaxelis_S3_007	Vesikari	Vaxelis	Infanrix hexa	Safety 3 Local AEs	1	•	•	•	•	•	•	D4	Measurement of the outcome
	Vaxelis_S4_008	Silfverdal	Vaxelis	Infanrix hexa	Safety 4 Fever	1	•	•	•	•	•	•	D5	Selection of the reported result
	Vaxelis_S4_007	Vesikari	Vaxelis	Infanrix hexa	Safety 4 Fever	1	•	•	•	•	•	•		
	Vaxelis_S4_6in1	Snape	Vaxelis	Infanrix hexa	Safety 4 Fever	1	•	•	•	Θ	•	•		
	Vaxelis_S5_008	Silfverdal	Vaxelis	Infanrix hexa	Safety 5 AESIs	1	•	•	•	•	•	•		
	Vaxelis_S5_007	Vesikari	Vaxelis	Infanrix hexa	Safety 5 AESIs	1	•	•	•	•	•	•		
	Vaxelis_55_6in1	Snape	Vaxelis	Infanrix hexa	Safety 5 AESIs	1	•	•	•	Θ	•	<u> </u>		