10 Conclusions

The safety data collected for IPV during the AP do not give rise to any concern about the safety of the vaccine. The benefit of vaccination by far outweighs the observed adverse events. Also when used in a Td-IPV combination vaccine the safety is not a concern.

The data presented is this PSUR lead to a proposal for adapting the SPC of IPV to add 'injection site redness' in addition to already mentioned 'swelling and pain at the injection site'. We propose to implement the change as soon as other changes in the SPC are necessary.

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APPENDIX 1. Core data sheet of IPV

Summary of product characteristics

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1 NAAM VAN HET GENEESMIDDEL

Poliomyelitisvaccin, suspensie voor injectie

2 KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING

Eén dosis van 0,5 ml poliomyelitisvaccin bevat de volgende actieve bestanddelen:

Geinactiveerd poliomyelitis virus type 1 (Maheney)*	40 D-antigeen eenheden
Geinactiveerd poliomyelitis virus type 2 (MEF 1)*	8 D-antigeen eenheden
Geinactiveerd poliomyelitis virus type 3 (Saukett)*	32 D-antigeen eenheden

Voor hulpstoffen, zie 6.1.

*) Gekweekt op Vero-cellen.

3 FARMACEUTISCHE VORM

Suspensie voor injectie. Het product is een suspensie van door formaline geinactiveerd en gezuiverd virus afgevuld als monodosis in ampullen of flesjes.

De kleur van het vaccin varieert van oranje-geel tot oranje-rood.

4 KLINISCHE GEGEVENS

4.1 Therapeutische indicaties

Actieve immunisatie tegen poliomyelitis.

4.2 Dosering en wijze van toediening

Eén dosis is 0,5 ml voor zowel kinderen als volwassen. Het vaccin wordt subcutaan of intramusculair toegediend. In het algemeen kan de primaire immunisatie vanaf de leeftijd van 2 maanden worden uitgevoerd. Een complete primaire immunisatie bestaat uit drie vaccinaties met elk 0,5 ml, de eerste twee worden gegeven met een interval van bij

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voorkeur 2 maanden doch minimaal 1 maand, de derde vaccinatie wordt 6-12 maanden na de tweede gegeven.

In Nederland worden kinderen bij voorkeur gevaccineerd volgens het Rijksvaccinatieprogramma met gecombineerd D(K)TP vaccin.

Personen die volledig tegen poliomyelitis zijn gevaccineerd en die vertrekken naar een gebied met verhoogd expositiegevaar aan poliomyelitis, wordt een revaccinatie met 1 dosis poliovaccin aangeraden ca. 1 maand voor vertrek, zeker wanneer de laatste enting 15 jaar of langer geleden heeft plaats gevonden.

4.3 Contra-indicaties

De algemene contra-indicaties die voor ieder vaccin gelden:

- ernstige reactie na eerdere vaccinatie met hetzelfde vaccin
- bekende overgevoeligheid voor een vaccincomponent.
- vaccinatie dient uitgesteld te worden bij ernstige met koorts gepaard gaande infecties

4.4 Bijzondere waarschuwingen en voorzorgen bij gebruik

De kleur van het vaccin varieert van oranje-geel tot oranje-rood. Vaccin met een duidelijk gele of violette kleur mag niet gebruikt worden.

Aangezien elke dosis sporen van neomycine, streptomycine en polymyxine B kan bevatten, is voorzichtigheid geboden bij de toediening van dit vaccin aan personen die overgevoelig zijn voor één van deze antibiotica.

Oudere kinderen en volwassenen kunnen flauwvallen na vaccinatie. Dit treedt meestal op korte tijd na vaccinatie en kan gepaard gaan met misselijkheid en braken. Indien flauwvallen bij eerdere vaccinaties is opgetreden of als er vóór of tijdens de toediening van het vaccin symptomen worden waargenomen die duiden op flauwvallen dan moet de persoon zittend of liggend worden gevaccineerd.

Poliomyelitis vaccin mag nooit intravasculair toegediend worden.

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Zoals bij alle injecteerbare vaccins dient tijdens het toedienen adequate medische behandeling beschikbaar te zijn, voor het geval zich na toediening van het vaccin anafylactische reacties voordoen. Zonodig worden epinefrine injecties en corticosteroïden gegeven, gedoseerd naar leeftijd en/ of lichaamsgewicht.

Het is mogelijk dat de verwachte immuunrespons uitblijft na vaccinatie van patiënten met aangeboren of verworven immuunstoornissen.

Het potentiële risico op apnoe en de behoefte om de respiratoire functies gedurende 48-72 uur te monitoren dient in beschouwing te worden genomen in het geval van primaire immunisatie bij zeer premature kinderen (geboren ≤ 28 weken zwangerschap), in het bijzonder voor kinderen met een nog niet volledig ontwikkeld ademhalingsstelsel in de anamnese. Aangezien het profijt van vaccineren in deze groep kinderen groot is, dient de vaccinatie niet onthouden of uitgesteld te worden.

4.5 Interacties met andere geneesmiddelen en andere vormen van interactie

Poliomyelitisvaccin kan gelijktijdig met andere vaccins worden toegediend, mits het op verschillende injectieplaatsen wordt toegediend.

4.6 Zwangerschap en borstvoeding

Gegevens betreffende een groot aantal zwangerschappen met blootstellingenaan poliomyelitisvaccin laten geen nadelig effect zien op de zwangerschap of op de gezondheid van de foetus/het pasgeboren kind. Echter poliomyelitisvaccin dient alleen tijdens de zwangerschap toegediend te worden, wanneer er een nadrukkelijk risico op besmetting is.
Poliomyelitisvaccin kan worden gebruikt tijdens de borstvoedingsperiode.

4.7 Beïnvloeding van de rijvaardigheid en van het vermogen om machines te bedienen

Het is niet waarschijnlijk dat poliomyelitisvaccin een effect heeft op de rijvaardigheid en het vermogen om machines te bedienen.

4.8 Bijwerkingen

Op basis van postmarketing gegevens (spontane meldingen) is vastgesteld dat de volgende bijwerkingen kunnen optreden. De bijwerkingen die gemeld zijn na vaccinatie met het poliomyelitisvaccin vonden meestal plaats gedurende de eerste drie dagen na vaccinatie en waren van tijdelijke aard.

Zenuwstelselaandoeningen

Zeer zelden (< 1/10.000): (Poly-) Neuropathie,

Ademhalingsstelsel-, borstkast- en mediastinumaandoeningen:

Ademhalingsproblemen (apnoe) bij zeer vroeg geboren kinderen (geboren ≤ 28 weken zwangerschap) (zie sectie 4.4).

Algemene aandoeningen en toedieningsstoornissen:

Lokale reacties:

Zelden (>1/10.000, <1/1.000): Zwelling, pijn op de injectieplaats.

Systemische reacties:

Zelden (>1/10.000, <1/1.000)): Koorts, malaise.

4.9 Overdosering

Er zijn geen gevallen van overdosering gerapporteerd.

5 FARMACOLOGISCHE EIGENSCHAPPEN

5.1 Farmacodynamische eigenschappen

Farmacotherapeutische categorie: Virale Vaccins, ATC-code: J07BF03

In dieren (apen of ratten) resulteert de toediening van het vaccin in de vorming van neutraliserende antistoffen.

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Immunogeniciteit in de mens

In mensen resulteert toediening van het vaccin in de vorming van antistoffen en het ontstaan van immunologisch geheugen; toediening van een tweede dosis van het vaccin resulteert in een secundaire respons gekarakteriseerd door een snelle stijging van antistof niveaus hetgeen wijst op de aanwezigheid van immunologisch geheugen.

Het antistof niveau is in het algemeen indicatief voor bescherming: Voor poliomyelitis is een titer (reciproke verdunning in neutralisatie test) ≥ 8 beschermend. Na de volledige serie vaccinaties worden in het algemeen bij de gevaccineerden beschermende antistof niveaus tegen poliovirus type 1, 2 en 3 bereikt.

In een onderzoek is bepaald wat het percentage seroprotectie in de algemene Nederlandse bevolking was in 1995-1996 (Immunity to Poliomyelitis in the Netherlands, Am. J. Epid., 2001;153, 3). Gedurende de decennia voorafgaand aan dit onderzoek was de vaccinatiegraad in het Rijksvaccinatieprogramma 97 % voor de primaire serie DKTP (3 doses op 3, 4 en 5 maanden). De leeftijd van de onderzochte personen lag tussen de 1 en 79 jaar. De mate van seroprotectie kan afhankelijk zijn van de tijdsduur na vaccinatie, die niet zo als in de meeste klinische studies standaard 1 maand is maar kan varieren afhankelijk van de leeftijd van de leeftijd van de persoon op het moment van bloedafname. Tevens wordt opgemerkt dat de data afkomstig zijn van het plain Poliomyelitisvaccin of combinatievaccin met een poliomyelitiscomponent. Het percentage seroprotectie is in de volgende tabel weergegeven.

	percentage seroprotectie (%)	95 % betrouwbaarheidsinterval
Polio type 1	96,6 %	95,9 - 97,2
Polio type 2	93,4 %	92,3 - 94,5
Polio type 3	89,7 %	88,3 -91,0

5.2 Farmacokinetische gegevens

Niet van toepassing voor vaccins.

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1.3.1. – SPC, Labelling and Package Leaflet

5.3 Gegevens uit het preklinisch veiligheidsonderzoek

Preklinische gegevens duiden niet op een speciaal risico voor mensen. Deze gegevens zijn afkomstig van conventionele studies op het gebied van veiligheidsfarmacologie en toxiciteit bij herhaalde dosering.

6 FARMACEUTISCHE GEGEVENS

6.1 Lijst van hulpstoffen

Formaldehyde (12,5 µg), 2-phenoxyethanol (2,5 mg), Medium 199 (0,1 ml) en verdunningsvloeistof en fosfaatbuffer (samen 0,08 ml) met de volgende samenstelling: natriumfosfaat, natriumchloride, kaliumchloride, magnesiumsulfaat, fenolrood en calciumchloride.

6.2 Gevallen van onverenigbaarheid

Niet van toepassing.

6.3 Houdbaarheid

24 maanden

6.4 Speciale voorzorgsmaatregelen bij bewaren

Bewaren bij 2 - 8 °C. Niet invriezen.

6.5 Aard en inhoud van de verpakking

Het vaccin is afgevuld in ampullen (type 1 hydrolytisch glas) of flesjes (type 1 hydrolytisch glas) afgesloten met een rubberen (latexvrij) stopje en een aluminium flip-off kapje en bevat 0,5 ml vaccin (voor 1 dosis).

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6.6 Speciale voorzorgsmaatregelen voor het verwijderen.

Geen bijzondere vereisten.

7 HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Nederlands Vaccin Instituut

Antonie van Leeuwenhoeklaan 11

3721 MA Bilthoven

030 2748010

8 NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Poliomyelitisvaccin is in het register ingeschreven onder RVG 17642

9 DATUM VAN EERSTE VERGUNNING / HERNIEUWING VAN DE VERGUNNING

25 augustus 1994

10 DATUM VAN HERZIENING VAN DE TEKST

Betreft volledige herziening: 21 juli 2008

Laatste gedeeltelijke herziening rubriek 4.2: 10 oktober 2008

APPENDIX 2. Line listings

In the tables presented in this appendix the main characteristics of all individual reports concerning SAEs and unlisted AEs are shown. Some explanatory notes to the labels of the table will follow hereafter.

Table 8 Explanatory notes to the line listings

Label	Explanatory notes
ID	Identity number of the case. For reports received via other parties, NVI adopts the ID
Source	Source of the report
Dose	Number of dose in the possible series of scheduled vaccinations (unk = unknown)
Vacdate	Date of administration of the vaccine (dd-mm-yyyy)
Age	Age of the patient in years (y), or months (mo), unk = unknown
S	Sex of the patient (f = female, m = male, unk= unknown)
Conc. medication	Concomitant medication at the time of vaccination
Report NVI	Date on which the report was received by NVI
V/S	Interval in days between vaccination and the first signs / symptoms (d= day, h= hour, min= minute, sec= second, wk= week, mo= month, y= year, unk = unknown)
Signs / symptoms	All single signs and symptoms that were reported. If the sign or symptom is unlisted, it is presented in *italic* typeface. †: see All signs and symptoms are listed in Table 5 and Table 6
C	Causality evaluated by NVI (U= unlikely; P= possible; N= not able to assess)
Medical intervention	If known, hospitalisation and/or medication given to treat the event(s) is listed
Outcome	Rec'd= recovered, rec'ing= recovering, rec'd/seq= recovered with sequelae, not rec'd= not recovered, unk=unknown
Comments	Any other relevant information

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Table 9 Line listing of all spontaneously reported SAEs (unlisted events are presented in italic typeface)

ID	Country	Source	Vaccine	Dose	Vacdate	Age Sex	Conc. medication	Report NVI	V/S	Signs / symptoms	C	Medical intervention	Outcome	Comments
									unk	*Raynaud's phenomenon*	N		not rec'd	
									unk	*necrosis*	N		not rec'd	
									unk	*inflammation*	N		not rec'd	
						51 y			unk	*morphoea*	N		not rec'd	
2006-0063	Germany	spontaneous	IPV	unk	28-04-2000	f	Td-pur	10-02-2006	unk	*antinuclear antibody increased*	N		unk	
									3 d	*pain in extremity*	P		rec'd	
				boo		40 y			3 d	*shoulder pain*	P		rec'd	
2006-0142	Germany	spontaneous	Td-IPV	ster	03-03-2006	f	none	17-03-2006	6 d	*muscular weakness*	P		rec'd	
						42 y			1 h	*facial paresis*†	U		rec'd	
2006-0250	Germany	spontaneous	Td-IPV	1	24-03-2006	m	none	13-04-2006	1 h	*paraesthesia oral*†	U		rec'd	
						58 y			9 d	*polyarthritis*	U		rec'd/seq	
2006-0345	Germany	spontaneous	IPV	unk	01-09-2005	m	Typhoral	22-05-2006	12 d	*C-reactive protein increased*	U		unk	
			IPV or											unclear which
2006-		spontan	Td or			42 y			7 wk	*Guillain-Barré syndrome*	U		rec'd	vaccine was
0710	Germany	eous	Td-IPV	unk	04-07-2002	m	none	22-08-2006	unk	*muscle atrophy*	U		not rec'd	administered
									< 1 d	*pain in head and neck*	U		rec'd	
									< 1 d	*nausea*	U		rec'd	
									< 1 d	*dyspnoea, subjective*	U		rec'd	
									< 1 d	*paraesthesia hands and lower thigh*†	U		rec'd	symptoms suggest a
									< 1 d	*feeling hot*	P		rec'd	circulatory reaction
		spontan				14 y			< 1 d	*heart rate increased*	U		rec'd	most likely related to
2006-0788	Germany	eous	Td-IPV	1	11-07-2006	f	none	17-10-2006	< 1 d	*blood pressure decreased*	U	hosp	rec'd	injection procedure
2006-		spontan				7mo								
1019	Germany	eous	IPV	unk	01-07-1998	f	none	05-12-2006	2 d	*convulsion*	U		rec'd	

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ID	Country	Source	Vaccine	Dose	Vacdate	Age Sex	Conc. medication	Report NVI	V/S	Signs / symptoms	C	Medical intervention	Outcome	Comments
2006-1109	Germany	spontaneous	Td-IPV	unk	04-12-2006	27 y f	none	29-12-2006	1 d 3 d 3 d 3 d 3 d 13 d	injection site pain *injected limb mobility decreased* *arthralgia* *radiculitis brachial*† *paresis*† *asthenia*	P P P P P P	hosp	not rec'd not rec'd not rec'd rec'd. rec'd not rec'd	
2007-0048	Germany	spontaneous	Td-IPV	unk	29-11-2001	13 y f		04-05-2007	15 d 15 d	*asthma* *cough*	U U	hosp	rec'd rec'd	
2007-0115	Germany	spontaneous	IPV	unk	03-08-2006	58 y f	Td	21-02-2007	16 d	*pancreatitis acute*	U	hosp	rec'ing	Td was administered 1 week later; other conc. med.: estradiol unk till 19-aug-06, amoxicillin 27-jul-06 / 5-aug-06 due to abscess of ear
2007-0583	Germany	spontaneous	Td-IPV	booster	16-07-2004	49 y m	Encepur (TBE virus)	02-07-2007	11 d 2 mo 2 mo >2.5 mo > 3 mo > 6 mo > 2.5 y unk unk unk unk unk	*muscle spasms* *NMR imaging abnormal* *muscle injury* *muscle contractions involuntary* *restless legs syndrome* *paraesthesia*† *intervertebral disc protrusion* *depressed mood* *abnormal sensation in eye* *dizziness* *malaise* *sleep disorder*	U U U U U U U U U U U U	hosp	rec'd/seq rec'd rec'd rec'd/seq rec'd rec'd/seq rec'd rec'ing rec'ing rec'ing rec'ing rec'd/seq	
2007-0677	Germany	spontaneous	Td-IPV	unk	19-06-2007	36 y f	-	26-07-2007	few h few h few h few h few h	*chills* *nausea* pyrexia *arthralgia* *urinary tract infection*	P P P N U	hosp	rec'ing rec'ing rec'ing rec'ing rec'ing	

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ID	Country	Source	Vaccine	Dose	Vacdate	Age Sex	Conc. medication	Report NVI	V/S	Signs / symptoms	C	Medical intervention	Outcome	Comments
2007-0877	Germany	spontaneous	Td-IPV	1	14-06-2007	54 y m	Encepur (TBE virus)	10-09-2007	4-5 h 4-5 h few h few h few h unk	pyrexia *chills* *chest pain* *dyskinesia, oral*† *dyspnoea* *C-reactive protein increased*	P P U U U U	hosp	rec'd rec'd rec'd rec'd rec'd rec'd	medical history: prolapsed disc, condition after myocarditis, recurrent convulsive thoracical complaints and psychovegetative dysregulation
2007-1289	Germany	spontaneous	Td-IPV	unk	feb 2007	unk m	none	14-11-2007	sec sec	*incorrect route of drug administration* *bursitis*	- U		rec'ing rec'ing	consumer report; event is caused by incorrect injection procedure and not by the vaccine
2008-0080	Spain	authority	IPV	unk	07-03-2008	6 y f	Infanrix	26-03-2008	< 1 d < 1 d < 1 d	fever injection site pain *injection site erythema*	P P P		unk unk unk	
2008-0081	Spain	authority	IPV	unk	07-03-2008	6 y m	Infanrix	26-03-2008	< 1 d < 1 d < 1 d	fever *headache* *injection site erythema*	P P P		rec'ing rec'ing rec'ing	
2008-0082	Spain	authority	IPV	unk	07-03-2008	6 y f	Infanrix	26-03-2008	< 1 d < 1 d	injection site pain *injection site erythema*	P P		unk unk	
2008-0083	Spain	authority	IPV	unk	07-03-2008	6 y m	Infanrix	26-03-2008	< 1 d < 1 d	*injection site erythema* injection site pain	P P		unk unk	
2008-0084	Spain	authority	IPV	unk	07-03-2008	6 y f	Infanrix	26-03-2008	< 1 d	*injection site erythema*	P		unk	

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ID	Country	Source	Vaccine	Dose	Vacdate	Age Sex	Conc. medication	Report NVI	V/S	Signs / symptoms	C	Medical intervention	Outcome	Comments
									< 1 d	injection site swelling	P		unk	
									1 d	*cranial neuropathy*†	P		unk	
									1 d	*neuralgia*†	P		rec'ing	
									1 d	*odynophagia*	U		rec'ing	
									1 d	*mastication disorder*	U		rec'ing	
									7 d	*CSF cell count increased*	U		unk	
									7 d	*CSF protein increased*	U		unk	
2008-0256	Germany	spontaneous	Td-IPV	1	06-12-2007	62 y m	none	05-03-2008	10 d	*facial paresis*†	P		unk	
									10 d	*hypoacusis*	U	hosp	unk	
2008-0694	Germany	spontaneous	IPV	unk	25-03-2008	43 y m	Mutagrip	30-04-2008	6 d	*VI th nerve paralysis*†	N	hosp	unk	
									< 2 h	*paraesthesia face*†	P		not rec'd	
									< 2 h	*facial pain*	P		not rec'd	
									2 h	*pain in jaw*	P		not rec'd	
									< 1 d	*hypoaesthesia facial*†	P		not rec'd	
									< 1 d	pyrexia	P		not rec'd	
									< 1 d	*feeling hot*	P		not rec'd	
									< 1 d	*headache*	U		not rec'd	
									< 1 d	*hyperhidrosis*	U		not rec'd	
									< 1 d	*neck pain*	U		not rec'd	
2008-1008	Germany	spontaneous	Td-IPV	booster	27-05-2008	22 y f	none	05-06-2008	< 1 d	*hyperreflexia*†	U		not rec'd	
									1 d	*chest discomfort*	U	hosp	rec'd	

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ID	Country	Source	Vaccine	Dose	Vacdate	Age Sex	Conc. medication	Report NVI	V/S	Signs / symptoms	C	Medical intervention	Outcome	Comments
									1 wk	*speech disorder*	U		rec'd	
									1 wk	*headache*	U		rec'd	
									few d	*psychomotor hyperactivity*†	U		rec'd	
									few d	*amnesia*	U		rec'd	
									few d	*csf cell count increased*	U		unk	
									few d	*blood brain barrier defect*	U		unk	
									few d	*vaccination complication*	U		rec'd	
									few d	*encephalitis*	U		rec'd	
									few d	*migraine with aura*	U		rec'd	
									few d	*mental disorder due to a general medical condition*	U		rec'd	
2008-1032	Germany	spontaneous	Td-IPV	bco ster	01-04-2008	23 y f		03-06-2008	few d	*paraesthesia hands*†	P	hosp	rec'd	
									< 1 d	apnoeic attack	P			
2008-1088	UK	spontaneous	IPV	1	06-05-2004	60 d f	DTwP-Hib Prevenar	20-06-2008	< 1 d	pyrexia 39.6	P			prematurely born infant
									< 1 d	*oxygen saturation decreased*	U		rec'd	
									3 wk	pyrexia	U		rec'd	
									3 wk	*arthritis reactive*	U		rec'd	consumer report,
									3 wk	*pain in extremity*	U		rec'd	medically confirmed;
									3 wk	*arthralgia*	U		rec'd	medical history:
									3 wk	*chills*	U		rec'd	coronary heart
									4 wk	*joint effusion*	U		rec'd	disease, hypertensive
									3 wk	*night sweats*	U		rec'd	heart disease,
									4 wk	*asthenia*	U		rec'd	tachyarrhythmia
2008-1885	Germany	spontaneous	Td-IPV	4	31-07-2008	56 y m		18-09-2008	4 wk	*C-reactive protein increased*	U	hosp	rec'd	absoluta, allergy to
									4 wk	*white blood cell count increased*	U	cortisone	rec'd	sulphonamide
										leukoencephalomyelitis	U		rec'd/seq	Mutagrip op 27-10-
										convulsion	U		rec'd/seq	2007, HepB boost
2008-2084	Germany	spontaneous	Td-IPV	1	16-11-2006	20 y f	none	10-10-2008	14 mo	*multiple sclerosis*	U	hosp	rec'd/seq	jan2008

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ID	Country	Source	Vaccine	Dose	Vacdate	Age Sex	Conc. medication	Report NVI	V/S	Signs / symptoms	C	Medical intervention	Outcome	Comments
										injection site pain	P		rec'd	
										dizziness	U		rec'd	
										oropharyngeal pain	U		rec'd	symptoms suggest a
										headache	U		rec'd	circulatory reaction
2008-2885	Czech Republic	spontaneous	IPV	5	05-12-2007	13 y f	none	28-11-2008	< 1 d	*cardiovascular insufficiency*	U		rec'd	most likely related to
										autonomic nervous system imbalance	U	hosp	rec'd	injection procedure

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Table 10 Line listing of all spontaneously reported AEs (unlisted events are presented in italic typeface)

ID	Country	Source	Vaccine	Dose	Vacdate	Age Sex	Conc. medication	Report NVI	V/S	Signs / symptoms	C	Medical intervention	Outcome	Comments
2006-0049	Germany	spontaneous	Td-IPV	unk	22-09-2005	17 y m		15-05-2006	1 d	fever	P		rec'd	
									1 d	*blood alkaline phosphatase increased*	U		rec'd	
									1 d	*γ-glutamyltransferase increased*	U		rec'd	
									1 d	*aspartate aminotransferase increased*	U		rec'd	
									1 d	*alanine aminotransferase increased*	U		rec'd	
									1 d	*leukopenia*	U		rec'd	
									1 d	*C-reactive protein increased*	U		rec'd	
2006-0517	Germany	spontaneous	Td-IPV	unk	13-06-2006	34 y f		14-11-2006	1 d	pyrexia 40	P		rec'd	
									1 d	*pain in extremity*	P		rec'd	
									3 d	*leukopenia*	U		rec'd	
									3 d	*thrombocytopenia*	U		rec'd	
									3 d	*C-reactive protein increased*	U		rec'd	
2006-0590	Germany	spontaneous	Td-IPV	unk	jul 2006	32 y f		14-11-2006	< 1 d	*ventricular extrasystoles*	U		unk	
2006-0626	Germany	spontaneous	Td-IPV	unk	11-07-2006	54 y f		14-11-2006	1 d	*injection site vesicles*	P		rec'd	
									1 d	*injection site erythema*	P		rec'd	
									1 d	injection site swelling	P		rec'd	
									1 d	injection site pain	P		rec'd	
									1 d	*injection site induration*	P		rec'd	
2006-0628	Germany	spontaneous	Td-IPV	unk	02-08-2006	31 y f		14-11-2006	1 d	injection site pain	P		rec'd	
									1 d	*injection site joint pain*	P		rec'd	
									1 d	*injected limb mobility decreased*	P		rec'd	
2006-0756	Germany	spontaneous	Td-IPV	unk	16-06-2006	58 y f		14-11-2006	1 d	*dermatitis allergic*	P		rec'd	
2006-0786	Germany	spontaneous	Td-IPV	unk	sept 2006	40 y f		19-02-2007	1 d	*injection site reaction*	P		rec'd	
									1 d	injection site pain	P		rec'd	

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ID	Country	Source	Vaccine	Dose	Vacdate	Age Sex	Conc. medication	Report NVI	V/S	Signs / symptoms	C	Medical intervention	Outcome	Comments
2006-0900	Germany	spontaneous	Td-IPV	unk	01-11-2006	70 y f		19-02-2007	4 d 4 d 4 d 4 d	*dizziness* *nausea* *arthropathy* body temperature increased	U U U U		rec'd rec'd rec'd rec'd	
2006-1122	Germany	spontaneous	IPV	unk	unk	unk m		23-11-2007	unk unk 1 d 1 d	pyrexia injection site pain *chills* *asthenia*	P P P P		rec'd rec'd rec'd rec'd	
2007-0119	Germany	spontaneous	Td-IPV	unk	jan/feb 2007	unk f		04-05-2007	1 wk	*urticaria*	U		rec'd	
2007-0176	Germany	spontaneous	Td-IPV	unk	26-02-2007	unk m		04-05-2007	2 d	*rash (itching papules)*	N		unk	no information on anatomic location or distribution
2007-0486	Germany	spontaneous	Td-IPV	unk	apr 2007	33 y f		28-08-2007	1-2 d 1-2 d 1-2 d	*general physical health deterioration* body temperature increased *headache*	P P P		rec'd rec'd rec'd	
2007-0830	Germany	spontaneous	Td-IPV	unk	05-07-2007	49 y m		23-11-2007	2 d	*rash maculo-papular axillary skin folds*	U		rec'd	
2007-0888	Germany	spontaneous	Td-IPV	unk	unk	unk f		23-11-2007	unk	*injection site reaction*	P		unk	
2007-1005	Germany	spontaneous	Td-IPV	unk	2007	unk m		23-11-2007	unk	*injection site reaction*	P		rec'd	
2007-1006	Germany	spontaneous	Td-IPV	unk	09-07-2007	53 y f		23-11-2007	1 d	*chills*	P		rec'd	
2007-1007	Germany	spontaneous	Td-IPV	unk	07-08-2007	29 y f		23-11-2007	min min	*circulatory collaps / syncope* *pallor*	U U		rec'd rec'd	symptoms suggest a circulatory reaction most likely related to injection procedure
2007-1568	Germany	spontaneous	Td-IPV	unk	28-11-2007	25 y f		26-02-2008	min min	*dizziness* *nausea*	U U		rec'd rec'd	

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ID	Country	Source	Vaccine	Dose	Vacdate	Age Sex	Conc. medication	Report NVI	V/S	Signs / symptoms	C	Medical intervention	Outcome	Comments
2008-0281	Germany	spontaneous	Td-IPV	unk	28-01-2008	unk f		20-05-2008	< 1 d	pyrexia	P		rec'd	
									< 1 d	*rash perioral*	P		rec'd	
									1 d	*influenza like illness*	P		rec'd	
2008-0327	Germany	spontaneous	Td-IPV	unk	12-11-2007	15 y m		20-05-2008	5 h	injection site pain	P		rec'd	
									5 h	*suprapubic pain*	U		rec'd	
									5 h	*hyperaesthesia*†	U		rec'd	
									< 1 d	*injection site erythema*	P		rec'd	
									36 h	*diplegia*† *(feeling of paralysis both legs)*	P		rec'd	
									36 h	*pain in extremity*	P		rec'd	
2008-0340	Germany	spontaneous	Td-IPV	unk	29-02-2008	27 y f		11-03-2008	3-4 h	*dysphagia*	U		rec'd	
									3-4 h	*respiratory disorder, subjectively*	U		rec'd	
									3-4 h	pyrexia 39.3	P		rec'd	
									3-4 h	*injected limb mobility decreased*	P		rec'd	
									< 1 d	injection site pain	P		rec'd	
2008-0832	Germany	spontaneous	Td-IPV	unk	26-04-2008	51 y f		19-08-2008	< 1 d	*pain*	P		rec'd	
									< 1 d	pyrexia	P		rec'd	
									< 1 d	*injection site erythema*	P		rec'd	
									< 1 d	injection site swelling	P		rec'd	
2008-0833	Germany	spontaneous	Td-IPV	unk	29-04-2008	42 y f		19-08-2008	1 d	malaise	P		rec'd	
									1 d	*pain*	P		rec'd	
									1 d	*injection site warmth*	P		rec'd	
									1 d	*injection site erythema*	P		rec'd	
									1 d	injection site swelling	P		rec'd	
2008-0834	Germany	spontaneous	Td-IPV	unk	29-04-2008	74 y f		19-08-2008	2 d	*general physical health deterioration*	P		rec'd	
									2 d	injection site swelling	P		rec'd	
									2 d	*injection site erythema*	P		rec'd	
									2 d	*nausea*	U		rec'd	
									3 d	*injection site infection*	P		rec'd	
2008-0871	Germany	spontaneous	IPV	unk	12-05-2008	8 y m		19-08-2008	1 d	*rash of face and throat*	P		rec'd	

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ID	Country	Source	Vaccine	Dose	Vacdate	Age Sex	Conc. medication	Report NVI	V/S	Signs / symptoms	C	Medical intervention	Outcome	Comments
2008-1079	Germany	spontaneous	Td-IPV	unk	05-06-2008	51 y f		19-08-2008	12 h 12 h 12 h 12 h	pyrexia 39 *chills* malaise *pain in extremity*	P P P P		rec'd rec'd rec'd rec'd	
2008-1283	Germany	spontaneous	Td-IPV	unk	1996	unk f		19-08-2008	unk	*dizziness* malaise	P P		rec'd rec'd	
2008-1284	Germany	spontaneous	Td-IPV	unk	1994	unk f		19-08-2008	12 h	*massive swelling injected upper arm*	P		rec'd	
2008-1297	Germany	spontaneous	Td-IPV	unk	23-06-2008	42 y f		19-08-2008	< 1 d < 1 d	*chills* pyrexia	P P		rec'd rec'd	
2008-1303	Germany	spontaneous	Td-IPV	unk	unk	unk unk		19-08-2008	unk unk	*chills* pyrexia	P P		rec'd rec'd	
2008-1316	Germany	spontaneous	Td-IPV	unk	jun 2008	unk m		19-08-2008	n.a.	*inappropriate schedule of drug administration*	-		n.a.	

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Periodic Safety Update Report 01 January 2009 – 31 December 2011

Periodic Safety Update Report for Poliomyelitisvaccin (Inactivated Poliomyelitis Vaccine, IPV)

Marketing authorisation number:	RVG 17642
Marketing authorisation holder:	Bilthoven Biologicals BV Antonie v Leeuwenhoeklaan 13 3721 MA BILTHOVEN The Netherlands
Manufacturer:	Nederlands Vaccin Instituut Antonie v Leeuwenhoeklaan 11 3720 AL BILTHOVEN The Netherlands
Period covered by this report:	1 January 2009 - 31 December 2011
International birth date:	25 August 1994
Date of report:	29 February 2012
Author(s):	Renée van Boxtel, MSc Pharmacovigilance Officer
Reviewed by:	Rudy Burgmeijer, MD, MPH Drug Safety Officer
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EXECUTIVE SUMMARY

Inactivated Poliomyelitis Vaccine (IPV) has been used in the Netherlands since 1961. Since 1962 the IPV component has been included in several combination vaccines that were used in the National Immunisation Program (NIP). From 1993 onwards, vaccines fell within the scope of the 'Wet op de Geneesmiddelenvoorziening'. Consequently, manufacturers of vaccines were obliged to apply for a marketing authorisation. The marketing authorisation for IPV was granted under RVG 17642 by the Dutch Medicines Evaluation Board as per 25 August 1994. This Periodic Safety Update Report (PSUR) includes all safety data on IPV from the time period 01 January 2009 to 31 December 2011, the analysis period (AP). The Netherlands Vaccine Institute (NVI) was marketing authorisation holder (MAH) of the product during the AP. From 10 January 2012 onwards, the marketing authorisation has been taken over by Bilthoven Biologicals BV (BBio).

During the AP 35 spontaneous and clinical reports were received from outside the Netherlands, in which a total of 98 AEs, including 54 SAEs, were reported. No clinical trials have been performed. No individual case histories describing serious adverse events (SAEs) associated with IPV were published.

The safety data collected for IPV during the AP did not give rise to concern about the safety of the vaccine.

Periodic Safety Update Report 01 January 2009 – 31 December 2011

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ABBREVIATIONS

AE	Adverse Event
AP	Analysis Period
BBio	Bilthoven Biologicals
CBG-MEB	College ter Beoordeling van Geneesmiddelen (Dutch Medicines Evaluation Board)
DLP	Data Lock Point
GBS	Guillain-Barré syndrome
ICH	International Conference on Harmonisation
Lareb	Netherlands Pharmacovigilance Centre
LTR	Laboratory for the Evaluation of the National Immunisation Program
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIP	National Immunisation Programme
NVI	Netherlands Vaccine Institute
PSUR	Periodic Safety Update Report
RIVM	National Institute for Public Health and the Environment
RMU	Regulatory & Medical Unit
RVG	Register of Medicinal Products
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SOC	System Organ Class

DEFINITIONS

Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. For a marketed drug, an adverse event will include those events occurring from a drug overdose, accidental or intentional, from drug abuse, those occurring from drug withdrawal and any reported failure of therapeutic effect.
Serious adverse event	Any untoward medical occurrence that at any dose: • results in death, • is life-threatening, • requires inpatient hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.
Life-threatening	The term "life-threatening" in the definition of "serious adverse event" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it had been more severe.
(Un)listed adverse event	Adverse event which is (not) mentioned in the company core safety information. Note: the terms (un)labelled, (un)expected and (un)listed are used as synonyms.
Related	An (serious) adverse event is considered to be related when there is a reasonable possibility of a causal relationship.
Spontaneous report	Report on (serious) adverse events observed during usual practice of a medicine (marketed use) and communicated in an unsolicited manner by any means.
Data lock point	The date designated as the cut-off date for data to be included in a periodic safety update report. This date is based on the international birth date.
International birth date	The date of the first marketing authorisation for a new medicinal product granted to any company in any country in the world.

1 Introduction

1.1 Scope of the periodic safety update report

This Periodic Safety Update Report (PSUR) on IPV has been drawn up in accordance with Directive 2001/83/EC, Volume 9A of the Rules Governing Medicinal Products in the European Union: Pharmacovigilance for Medicinal Products for Human Use, and the ICH E2C guideline on PSURs for Marketed Drugs and the Addendum of this guideline, adopted on 25 April 2003.

The safety information compiled in this report includes all safety data from the entire territory of marketing of the product, which were made known to the Netherlands Vaccine Institute (NVI), Bilthoven, The Netherlands. This report covers the time period from 1 January 2009 to 31 December 2011, the analysis period (AP). Data lock point: 31 December 2011. NVI has been marketing authorisation holder (MAH) during the entire AP. From 10 January 2012 onwards, the marketing authorisation has been taken over by Bilthoven Biologicals BV (BBio).

1.2 Product characteristics

Inactivated trivalent poliomyelitis vaccine (IPV) is a suspension of purified and formalin inactivated poliomyelitis viruses containing the three types of poliomyelitis virus: type 1: strain Mahoney; type 2: strain MEF 1; type 3: strain Saukett. The virus is cultured on Vero cells. IPV is a suspension for injection that can be used subcutaneously or intramuscularly. IPV was supplied in glass vials as a single dose of 0.5 ml.

IPV is indicated for active immunisation against poliomyelitis. In the Netherlands it has been licensed for primary immunisation of adults, children and infants from the age of 2 months. A complete immunisation schedule consists of 3 doses, given with an interval of preferably 2 months, but at least 1 month between the first and the second dose, followed by a third dose (booster) 6 to 12 months after the second dose.

In the Netherlands, plain IPV (i.e., not as a component in a combination vaccine) is almost exclusively used in adults, because the National Immunisation Programme (NIP) for infants and children does not contain the plain IPV. Instead, a poliomyelitis component of different manufacturers is included in several combination vaccines in the NIP. IPV from NVI is a component of the NVI combination vaccine Tetanus-, Diphtheria-, Poliomyelitis vaccine (Td-IPV). Td-IPV is licensed for the Dutch

market under no. RVG 17641 ('DTP-vaccin') and is therefore addressed in a separate PSUR.

2 Worldwide market authorisation status

IPV has been authorised for marketing in the Netherlands under marketing authorisation number RVG 17642 on 2 December 1993 during the entire period covered by this PSUR.

Bulk IPV and/or final lot IPV are also exported to several EU and non-EU countries. In those countries other companies than NVI are MAH of the product. IPV may be part of combination vaccines in some countries, see Table 1.

Table 1 Marketing authorisation status of IPV worldwide

Country	MAH	Formulations licensed
The Netherlands	NVI	IPV Td-IPV[1]
Germany	Other	IPV Td-IPV
India	Other	IPV DTwP-Hib-IPV
Republic of Korea	Other	IPV

[1] Td-IPV is licensed separately from IPV on the Dutch market under no. RVG 17641 ('DTP-vaccin') and is therefore addressed in a separate PSUR.

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3 Update of regulatory authority or MAH actions taken for safety reasons

During the AP no actions for safety reasons were initiated by any regulatory authority or NVI (MAH) for IPV.

4 Changes to reference safety information

The currently approved SmPC for IPV, dated 5 January 2012, is included in appendix 1. There have been two updates of the SmPC during the AP with minimal changes.

One change concerned the addition of 'injection site redness' in the 'Undesirable effects' section 4.8 as a result from the previous PSUR in MedDRA frequency category '*rare*' (> 1/10,000, < 1/1,000).

The other change regarded a slightly altered description of the primary vaccination schedule in the 'Posology and method of administration' section 4.2:

> *Old text: In general the primary immunisation can be given from the age of 2 months. A complete immunisation schedule consists of 3 doses, given with an interval of preferably 2 months, but at least 1 month between the first and the second dose, followed by a third dose (booster) 6 to 12 months after the second dose.*
>
> *New text: A primary vaccination schedule consists of 3 doses poliomyelitis vaccine, to be administered with a minimum interval of 4 weeks. Children receive these 3 vaccinations during the first 6 months of the first year of life. After completion of the first series of vaccinations a booster dose can be given with an interval of at least 6 months. If local authorities use a vaccination schedule that starts before the age of 2 months, and/or if the interval between the administered is less than 8 weeks, then a booster dose should be administered, but not before the age of 9 months.*

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5 Patient exposure

5.1 Market use

The total patient's exposure to IPV during the AP is not exactly known but can be estimated based on total number of doses distributed. In the Netherlands 1,003 doses were sold during the AP.

NVI-produced IPV is also exported either as trivalent bulk or final bulk to companies in other countries, where it can either be formulated as plain IPV or as an IPV-containing combination vaccine. NVI is not the marketing authorisation holder of IPV in those countries. For informational purposes, knowledge of (S)AEs are mutually exchanged between NVI and the MAHs, this includes IPV-containing combination vaccines. The exposure to IPV in other countries is estimated to mount to a total 7,168,834 doses (= doses sold) as shown in Table 2. Thus the world-wide use of NVI-produced IPV greatly exceeds the use of plain IPV in The Netherlands.

Table 2 Number of IPV doses marketed during the AP

Country	Number of doses
The Netherlands	1,003
Germany	669,822
India	5,020,000
Republic of Korea	1,377,000
Unicef[1]	101,009
Total	**7,168,834**

[1] *procurement by Unicef Supply Division, Copenhagen, Denmark; country(ies) where distributed unknown*

5.2 Clinical trials

During the AP no clinical trials were performed with IPV by NVI.

6 Presentation of individual case histories

In Table 3, an overview is presented of reports of adverse events (AEs) and serious adverse events (SAEs) obtained from spontaneous reports, clinical trials, literature and other sources during the AP. The numbers are stratified by plain IPV or IPV-containing combination vaccines (see section 5.1).

Table 3 Overview of number of reports of AEs and SAEs, categorized by source and stratified by plain IPV or IPV-containing combination vaccines

Source	Reports of AEs		Reports of SAEs		Total	
	IPV	IPV-combi	IPV	IPV-combi	IPV	IPV-combi
Spontaneous reports*	6	8	9	4	15	12
Clinical studies*	1	1	3	3	4	4
Literature*	-	-	-	-	-	-
Other sources	-	-	-	-	-	-
Total	7	9	12	8	19	17
Total (both vaccine types)	16		19		35	

** not within marketing authorisation territory, see paragraph 6.1.1*

Table 4 shows an overview of the number of listed and unlisted adverse events classified by seriousness. The numbers are stratified by plain IPV or IPV-containing combination vaccines (see section 5.1). Line listings of all reported SAEs and AEs can be found in Appendix 2.

Table 4 Overview of number of listed and unlisted adverse events, classified by seriousness and stratified by plain IPV or IPV-containing combination vaccines

Source	AEs		SAEs	
	IPV	IPV-combi	IPV	IPV-combi
Listed	10	10	3	1
Unlisted	4	20	38	12
Total	14	30	41	13
Total (both vaccine types)	44		54	

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6.1 Relevant individual case reports from spontaneous reports, clinical trials, published individual case histories, and case reports from other sources

6.1.1 Spontaneous (serious) adverse event reports

During the entire AP no spontaneous reports of (serious) adverse events of plain IPV were made known to NVI within the marketing authorisation territory. However, copies of 35 spontaneous (S)AE reports of plain IPV and IPV-containing combination vaccines were forwarded to NVI by other MAHs, of which 11 from non-EU. Nineteen reports regarded IPV, whereas 16 reports concerned IPV-containing combination vaccines.

6.1.2 Relevant individual case reports from clinical trials

Two clinical trials are being performed in India by the local MAH, entitled *'A randomized, multicenter, open label, comparative study to evaluate the immunogenicity and reactogenicity of a new fully liquid hexavalent DTwP-Hepb-Hib-IPV vaccine (EasySix™, Panacea Biotec Ltd.) with pentavalent DTwP-Hepb/Hib vaccine (Tritanrix-HB™ reconstituted with Hiberix™, GSK) co-administered with Imovax Polio (Salk based inactivated polio vaccine; Sanofi Pasteur India Pvt. Ltd.) in healthy infants'*; and *'A randomized, multicenter, open label, comparative study to evaluate the immunogenicity and reactogenicity of a new fully liquid pentavalent DTwP-Hib-IPV vaccine (EasyfourPol™, Panacea Biotec Ltd.) with tetravalent DTwP/Hib vaccine (TetrAct-Hib™) co-administered with Imovax Polio (Salk based inactivated polio vaccine; Sanofi Pasteur India Pvt. Ltd.) in healthy infants'* (personal communication). The trials are still ongoing. Sofar 8 individual case reports have been forwarded. Four reports concerned IPV, 3 a DTwP-Hib-IPV combination vaccine, and one a DTwP-HepB-Hib-IPV combination vaccine.

6.1.3 Published individual case histories

No individual case histories describing an SAE associated with the use of IPV was published during the AP in literature reports.

6.1.4 Relevant serious adverse event reports received via other sources

No relevant serious adverse event reports were received via other sources.

6.2 Summary tabulations on spontaneous serious and non-serious adverse events

During the AP a total of 98 AEs were reported, of which 54 were classified as serious. Of these 54 SAEs, when stratified by plain IPV or IPV-containing combination vaccines, 41 SAEs were reported after plain IPV administration, and 15 after IPV-containing combination vaccines. The reason for SAE classification of the reports was hospitalisation in 12 cases, medically significant in 6 cases and unknown in 1 case. A summary listing of all listed and unlisted SAEs is presented in Table 5, categorised by MedDRA system organ class (SOC). All reported listed and unlisted AEs are presented in the same way in Table 6. Line listings of the reports can be found in Appendix 2.

Table 5 Summary listing of all spontaneously reported, listed and unlisted SAEs, categorised by MedDRA system organ class (SOC), and distribution by plain IPV or IPV-containing combination vaccines.

MedDRA system organ class	Number of SAEs							
Preferred term	2009		2010		2011		Total per SOC	
	IPV	IPV comb	IPV	IPV comb	IPV	IPV comb	IPV	IPV comb
Infections and infestations							3	1
breast abscess*			1					
infection susceptibility increased*					1			
upper respiratory tract infection*					1			
Blood and lymphatic system disorders							1	1
haemolytic anaemia *		1						
ITP *					1			
Endocrine disorders							1	-
autoimmune thyroiditis*			1					
Metabolism and nutrition disorders							1	-
diet refusal*	1							
Nervous system disorders							7	3
dyskinesia*			1					
Guillain-Barré syndrome*		1						
hypopallaesthesia*			1					
hyporeflexia*			1					
hypotonic hyporesponsive episode*						1		
migraine*			1					
paraesthesia hands			1					
paralysis transient*		1						
somnolence*	2							
Eye disorders							2	-
eye inflammation*					1			
eye pruritus*			1					
Ear and labyrinth disorders							1	-
acute hearing loss*			1					
Cardiac disorders							1	1
congestive heart failure*						1		
tachycardia*	1							
Vascular disorders							4	-
cyanosis*					1			
hypotension*					1			
pallor*					2			
Respiratory, thoracic and mediastinal disorders							2	2
bronchopneumonia*						2		
cough*					1			
hyperventilation*			1					

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Gastrointestinal disorders							7	-
diarrhoea*	3							
loose motions*	1							
retching*					1			
vomiting*	2							
Hepatobiliary disorders							-	1
choledocholithiasis*		1						
Skin and subcutaneous tissue disorders							1	-
pruritus*			1					
Musculoskeletal and connective tissue disorders							4	2
arthralgia*		1						
fibromyalgia*			1					
muscle twitching*			1					
muscular weakness*			1					
myalgia*		1						
tendon pain*			1					
General disorders and administration site conditions							5	3
fatigue*		1	1					
fever	2	1						
gait disturbance*			1					
influenza like illness*		1						
irritable*	1							
Social circumstances							1	-
walking aid use*			1					
Total	**13**	**12**	**18**	**-**	**10**	**4**	**41**	**16**

* unlisted events

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Table 6 Summary listing of all spontaneously reported, listed and unlisted AEs, categorised by MedDRA system organ class (SOC), and distribution by plain IPV or IPV-containing combination vaccines.

MedDRA system organ class	Number of AEs							
Preferred term	2009		2010		2011		Total per SOC	
	IPV	IPV comb	IPV	IPV comb	IPV	IPV comb	IPV	IPV comb
Investigations							-	2
blood urine present*		1						
C-reactive protein increased*		1						
Nervous system disorders							-	2
paraesthesia		1						
speech disorder*		1						
Ear and labyrinth disorders							-	1
hypoacusis*		1						
Cardiac disorders							-	2
cardiovascular disorder*		1						
tachycardia*		1						
Vascular disorders							-	2
dizziness*		1						
hypotension*		1						
Gastrointestinal disorders							-	2
nausea*		1						
vomiting*		1						
Skin and subcutaneous tissue disorders							2	1
rash generalised*	1							
rash pustular*		1						
skin discolouration*	1							
Musculoskeletal and connective tissue disorders							-	1
muscle spasms*		1						
General disorders and administration site conditions							12	17
body temperature increased		1						
feeling hot		1						
fever	3	1	1					
hyperhidrosis*		2						
influenza like illness*								
injected limb mobility decreased*		2						
injection site erythema	1	1						
injection site induration*	1					1		
injection site inflammation*		1						
injection site pain	1	4	1		1			
injection site pruritus*	1							
injection site reaction*		1						
injection site swelling	1	2	1					
Total	10	29	3	-	1	1	14	30

* unlisted events

7 Studies

7.1 Newly analysed studies

No relevant (clinical) studies were performed or analysed by NVI during the AP.

7.2 Targeted new safety studies

No safety studies were targeted by NVI during the AP.

7.3 Published safety studies

No data from non-clinical, clinical or epidemiological trials revealing relevant new safety information were published during the AP.

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8 Other information

8.1 Efficacy-related information

No data concerning lack of efficacy of IPV came to our knowledge during the AP. No cases of poliomyelitis are reported in The Netherlands in vaccinated people.

8.2 Late-breaking information

No relevant additional information was received after the data lock point.

9 Overall safety evaluation

9.1 Reported serious adverse events

During the AP, no spontaneous reports of (S)AEs of plain IPV were received that originated from the marketing authorisation territory (The Netherlands). This is not a surprising finding in view of the very low exposure; in the NIP, IPV is not used as a single component but is always part of a combination vaccine.

Since other MAHs use IPV bulk or IPV final product manufactured by NVI it is considered appropriate to evaluate the forwarded reports by our export partners. The forwarded reports contained (S)AEs after administration of plain IPV, and also after administration of IPV-containing combination vaccines. There does not seem to be a difference in type of adverse events for the combination vaccine or the plain vaccine, as far as the small numbers allow such a statement.

Table 5 shows the distribution of the SAEs reported during the AP categorised by MedDRA SOC. During this period a total number of 54 SAEs (41 for plain IPV and 15 for IPV-containing combination vaccines) were reported, concerning 19 vaccinees (12 received plain IPV and 7 received an IPV-containing combination vaccine). The calculated SAE incidence is 19 reports in 7,168,834 doses, corresponding to 0.75 per 100,000 doses, or 0.27 patients per 100,000 doses for whom an SAE is reported.

In general, there is no specific pattern among the unlisted SAEs, and the majority of the unlisted SAEs occurred no more than once. The MedDRA SOCs with the highest number of SAEs occurring were *Nervous system disorders* (10), and *General disorders and administration site conditions* (8). In 6 of 19 patients the SAEs were evaluated as probably or possibly related (4 for plain IPV, 2 for IPV-containing combination vaccines). In 13 cases the SAEs were evaluated as unlikely related to the vaccination, or there were insufficient data for a causality assessment. Most of the unlisted SAEs are isolated cases that are unlikely related, and therefore seem to be of little relevance to the safety of the vaccine.

We conclude that the incidence of reported SAEs is low and that they do not cause any concern about the safety of IPV.

Details of the reported SAEs are described in the following paragraphs, and a line listing can be found in Appendix 2.

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9.1.1 Plain IPV SAEs

2009-1402 and 2009-1403: The two reported SAEs (linked cases) were assessed as medically significant by the reporter. The described symptoms, somnolence directly after the vaccination for a short period, occurring in two infants, may possibly be related to the vaccination, but do not cause any concern about the safety of IPV.

C-055, D-029 and D-080: Three SAEs were reported in a clinical trial in India. All three cases were judged as unrelated to the vaccination. The cases involved diarrhoea after 1 day (1 case) and after 9 days (2 cases) and were likely due to gastrointestinal infections. All children were hospitalised and recovered or were recovering at the time of reporting.

2010DE04549: This case concerned a spontaneous report of acute hearing loss 3 days after vaccination in a 32-year old female. No more details were available, therefore causality could not be assessed. Acute hearing loss has earlier not been reported after vaccination with IPV. This isolated report does not lead to a new safety concern.

2010DE52935: This case concerned a 44 year-old female who received several vaccinations between 1989 and 2004, of which 1 dose of IPV in January 2000. In 1990 the patient presented with generalised muscle weakness and migraine, muscle weakness in arms and legs in 2000, muscle weakness predominantly in arms and legs in 2003, and worsened muscle weakness in arms and legs following vaccination and needed a walking cane in 2004. Examinations were compatible with autoimmune thyroiditis with hypothyroidism. There is no known pathomechanism to explain a causal relationship with IPV vaccination, and a temporal relationship is uncertain. Therefore the case is assessed as unlikely related.

2010DE67831: This case concerned a 32-year old female who received a first dose of IPV. Three and a half months later, the patient presented with an abscess in the breast (side not indicated). The patient was hospitalized and underwent repeated surgical interventions because of the abscess. The patient received homeopathic therapy (unspecified). The final outcome of the event was reported as completely resolved. Breast abscess is unlisted. Due to the long latency between vaccination and the event and the lack of a biological plausible mechanism, the event is assessed as unlikely related.

2010DE80154: This case concerned a 47 year-old female who experienced slight itching on the day of simultaneous IPV vaccination and diphtheria vaccination, and itchy eyes one day later. Itching and itchy eyes are unlisted. Due to a close time-event relationship, causality is assessed as possible. Nine days later the patient experienced tingling in hands, and later on the same day hyperventilation, for which she was