Periodic Safety Update Report 01 January 2006 – 31 December 2008

Periodic Safety Update Report for Inactivated Poliomyelitis Vaccine (IPV)

Marketing authorisation number:	RVG 17642
Marketing authorisation holder:	Nederlands Vaccin Instituut (NVI) Antonie v Leeuwenhoeklaan 11 3721 MA BILTHOVEN The Netherlands
Period covered by this report:	01 January 2006 - 31 December 2008
International birth date:	1961
Date of report:	16 February 2009
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Bilthoven, February 2009

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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 2 December 1993. This Periodic Safety Update Report (PSUR) includes all safety data on IPV from the time period 01 January 2006 to 31 December 2008, the analysis period (AP). The Netherlands Vaccine Institute (NVI) was marketing authorisation holder (MAH) of the product during the AP. During the AP no clinical trials were performed and no individual case histories describing serious adverse events (SAEs) or non-serious unlisted adverse events (AEs) 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, however the addition of injection site erythema in the next update of the summary of product characteristics (SPC) is proposed.

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ABBREVIATIONS

AE	Adverse Event
AP	Analysis Period
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
SPC	Summary of Product Characteristics

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. 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 Regulatory & Medical Unit (RMU) of the Netherlands Vaccine Institute (NVI), Bilthoven, The Netherlands. This report covers the time period from 1 January 2006 to 31 December 2008, the analysis period (AP). Data lock point: 31 December 2008.

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. IPV is a suspension for injection that can be used subcutaneously or intramuscularly. The IPV batches that were released on the Dutch market during the AP were cultured on monkey kidney cells. IPV was supplied in glass vials as a single dose of 1 ml, in the Netherlands. In 2004 approval was obtained from the Dutch Medicines Evaluation Board (CBG-MEB) to culture the virus on Vero cells, change the formulation buffer and concentrate the vaccine to a 0.5 ml dose.

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 is included in several combination vaccines from both NVI and other manufacturers 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	Marketed during AP
The Netherlands	NVI	IPV[1] Td-IPV[2]	2006-2008
Germany, Italy, Switzerland	Other than NVI	IPV[1] Td-IPV[1]	2006-2008
Spain, Austria	Other than NVI	IPV	2006-2008
Ukrain	Other than NVI	IPV	Not marketed yet
India	Other than NVI	IPV	2008
South-Korea	Other than NVI	IPV	Not marketed yet

[1] *IPV produced on monkey kidney cells*

[2] *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.*

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.

The class labelling text on the risk of apnoea following vaccination of very prematurely born infants was included in the SPC as agreed by the CHMP in July 2007 (see section 4).

4 Changes to reference safety information

The currently approved SPC for IPV, dated 10 October 2008, is included in appendix 1. There have been two updates of the SPC during the AP. The most relevant change was based on findings of the previous PSUR and is cited below:

- Nervous system disorders: '*very rare*' (< 1/10,000): (Poly) Neuropathy (added in section 4.8)

Reports of (poly)neuropathy during the AP of this PSUR are considered as listed, since the adverse event was acknowledged as an undesirable effect since the previous PSUR.

Other changes that were implemented, either as a result of revisions of the QRD template, class-related additions imposed by the authorities, or for other reasons are:

- The potential risk of apnoea and the need for respiratory monitoring for 48 -72 h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed. (added in section 4.4)
- Respiratory, thoracic and mediastinal disorders: Difficulty breathing (apnoea) in very prematurely born infants (born ≤ 28 weeks pregnancy) (added in section 4.8)
- Older children and adults may faint after vaccination. Usually this occurs shortly after the vaccination and may be accompanied by nausea or vomiting. If a person has fainted during previous vaccinations or when prior to or during the administration of the vaccine symptoms are observed that indicate imminent fainting, that person should be vaccinated in a sitting or supine position. (added in section 4.4)
- Since every dose may contain traces of neomycin, streptomycin and polymyxin B, caution should be exercised upon administration of this vaccine to persons who are hypersensitive to one of these antibiotics. (added in section 4.4)
- Poliomyelitis vaccine may be administered simultaneously with other vaccines, if administered on different injection sites. (added in section 4.5)
- Data concerning a large number of pregnancies with exposure to poliomyelitis vaccine do not show any adverse effect on the pregnancy or on the health of the foetus/the newborn child. However poliomyelitis vaccine should only be administered during pregnancy when there is an urgent risk of infection. Poliomyelitis vaccine can be used during lactation.

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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 2,533 doses were sold during the AP. NVI-produced IPV is also exported either as bulk product or final product to other countries. The exposure to IPV in other countries is estimated to mount to a total of 4,436,131 possible doses (= doses sold). Thus the world-wide use of NVI-produced IPV greatly exceeds the use of plain IPV in The Netherlands. It is reasonable though to assume that in India, where bulk IPV is delivered by NVI, the actual distribution numbers may lag well behind the export numbers, because IPV has just recently entered the market. Furthermore it is obvious that when bulk IPV is exported, some timé is required for the formulation, filling process and subsequent release of the final product. So in order to be on the safe side for the calculations of the incidence of SAEs, we only included the doses sold to those countries where we know the vaccine is actually on the market. Thus the estimated distributed number of doses mounts up to 1,686,131.

In Germany, Italy and Switzerland IPV may have been formulated in a Td-IPV combination vaccine in a substantial amount of sold doses (tetanus and diphtheria toxoid are derived from another manufacturer, so not identical to Td-IPV from NVI). Reports on this IPV-containing combination vaccine are included in this PSUR.

Table 2 Number of IPV doses sold during the AP

Country	Number of doses
The Netherlands	2,533
Germany/Italy/Switzerland	1,611,979
Spain/Austria	20,619
India	2,750,000
Unicef[1]	51,000
Total	**4,436,131**

[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.

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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 the Td-IPV combination vaccine (see section 5.1, last paragraph).

Table 3 Overview of number of reports of AEs and SAEs, categorized by source and stratified by plain IPV or the Td-IPV combination vaccine

Source	Reports of AEs		Reports of SAEs		Total	
	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV
Spontaneous reports*	2	29	7	14	9	43
Clinical studies	-	-	-	-	-	-
Literature	-	-	-	-	-	-
Other sources	-	-	5	-	5	-
Total	2	29	12	14	14	43
Total (both vaccine types)	31		27**		58**	

** not within marketing authorisation territory, see paragraph 6.1.1*
*** one additional SAE report is counted in which the administered vaccine was either IPV, Td-IPV or Td.*

Table 4 shows an overview of the number of listed and unlisted AEs classified by seriousness. The numbers are stratified by plain IPV or the Td-IPV combination vaccine (see section 5.1, last paragraph). 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 the Td-IPV combination vaccine

Source	AEs		SAEs	
	IPV	Td-IPV	IPV	Td-IPV
Listed	2	24	10	19
Unlisted	3	57	22	70
Total	5	81	32	89
Total (both vaccine types)	86		121	

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 53 spontaneous SAE reports of plain IPV and the combination vaccine Td-IPV were forwarded to NVI by another EU MAH. Nine reports regarded IPV, whereas 43 reports concerned the combination vaccine Td-IPV. In one other report the administered vaccine was either IPV, the Td-IPV combination or Td. The other non-EU MAHs have declared that no reports of adverse events were received during the AP.

6.1.2 Relevant individual case reports from clinical trials

Not applicable since no clinical trials with IPV were performed.

6.1.3 Published individual case histories

No individual case histories describing SAEs and non-serious unlisted AEs associated with the use of IPV were published during the AP in literature reports.

6.1.4 Relevant serious adverse event reports received via other sources

Five authority SAE reports on IPV were forwarded by another EU MAH..

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

During the AP 207 AEs were reported, among them 121 SAEs. When stratified by plain IPV or Td-IPV combination, 32 SAEs were reported after plain IPV administration, and 89 after a Td-IPV combination. The reason for SAE classification of the reports was hospitalisation in 14 cases, medically significant in 11 cases and possibly lasting damage in 2 cases. A summary listing of all listed and unlisted SAEs is presented in Table 5, categorised by MedDRA system organ class. 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.

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Table 5 Summary listing of all spontaneously reported, listed and unlisted SAEs, categorised by MedDRA system organ class, and distribution by plain IPV or the Td-IPV combination administration (see section 5.1, last paragraph).

MedDRA system organ class	Number of SAEs									
Preferred term	2006		2007		2008		Total per SAE		Total per SOC	
	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV
Investigations									2	8
antinuclear antibody increased*	1						1			
CSF protein increased*						1		1		
C-reactive protein increased*	1			1		1	1	2		
CSF cell count increased*						2		2		
NMR imaging abnormal*				1				1		
oxygen saturation decreased*						1		1		
white blood cell count increased*						1		1		
Cardiac disorders									0	2
blood pressure decreased*		1						1		
heart rate increased*		1						1		
Nervous system disorders									6	28
amnesia*						1		1		
blood brain barrier defect*						1		1		
convulsion*	1					1	1	1		
cranial neuropathy right side†						1		1		
dyskinesia, oral†				1				1		
dizziness*				1	1		1	1		
encephalitis*						1		1		
facial paresis†		1				1		2		
Guillain-Barré syndrome*	1						1			
headache*					2	2	2	2		
hyperreflexia†						1		1		
hypoaesthesia facial†						1		1		
leukoencephalomyelitis*						1		1		
mastication disorder*						1		1		
migraine with aura*						1		1		
multiple sclerosis*						1		1		
neuralgia nervus occipitalis right head and throat†						1		1		
paraesthesia calf, thigh, hands†				1				1		
paraesthesia face†						1		1		
paraesthesia hands and/or lower thigh†		1				1		2		
paraesthesia oral†		1						1		
paresis†		1						1		
psychomotor hyperactivity†						1		1		
radiculitis brachial†		1						1		
restless legs syndrome*				1				1		
speech disorder*						1		1		
VI th nerve paralysis†					1		1			

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MedDRA system organ class / Preferred term	Number of SAEs									
	2006		2007		2008		Total per SAE		Total per SOC	
	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV
Eye disorders									0	1
abnormal sensation in eye*				1				1		
Ear and labyrinth disorders									0	1
hypoacusis *						1		1		
Respiratory, thoracic and mediastinal disorders									1	6
apnoeic attack					1		1			
asthma*		1						1		
chest discomfort*						1		1		
chest pain*				1				1		
cough*		1						1		
dyspnoea*				1				1		
dyspnoea, subjective*		1						1		
Gastrointestinal disorders									2	3
nausea*		1		1				2		
odynophagia*						1		1		
oropharyngeal pain*					1		1			
pancreatitis acute*			1				1			
Renal and urinary disorders									0	1
urinary tract infection*				1				1		
Skin and subcutaneous tissue disorders									1	0
morphoea*	1						1			
Musculoskeletal and connective tissue disorders									2	16
arthralgia*		1		1		1		3		
arthritis reactive*						1		1		
bursitis*				1				1		
intervertebral disc protrusion*				1				1		
joint effusion*						1		1		
muscle atrophy*	1						1			
muscle contractions involuntary*				1				1		
muscle injury*				1				1		
muscle spasms*				1				1		
muscular weakness*		1						1		
neck pain*						1		1		
pain in extremity*		1				1		2		
pain in jaw*						1		1		
polyarthritis*	1						1			
shoulder pain*		1						1		
Injury, poisoning and procedural complications									0	1
incorrect route of drug administration*				1				1		
Vascular disorders									3	0
cardiovascular insufficiency*					1		1			
necrosis, acral*	1						1			
Raynaud's phenomenon*	1						1			
General disorders and administration site conditions									15	19

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MedDRA system organ class	Number of SAEs									
Preferred term	2006		2007		2008		Total per SAE		Total per SOC	
	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV
asthenia*		1				1		2		
autonomic nervous system imbalance*					1		1			
chills*				2		1		3		
facial pain*						1		1		
feeling hot*		1				1		2		
hyperhidrosis*						1		1		
inflammation finger tips*	1						1			
injected limb mobility decreased*		1						1		
injection site erythema*					5		5			
injection site pain	1				4		5			
injection site swelling						1		1		
malaise				1				1		
night sweats*						1		1		
pain*		1						1		
pyrexia			1	2	2	3	3	5		
Psychiatric disorders									0	3
depressed mood*				1				1		
mental disorder due to a general medical condition*						1		1		
sleep disorder*				1				1		
Total	11	19	2	25	13	45	32	89	32	89

* unlisted events
† unlisted but possible symptom of (poly)neuropathy, see section 9.1

Table 6 Summary listing of all spontaneously reported, listed and unlisted AEs, categorised by MedDRA system organ class, and distribution by plain IPV or the Td-IPV combination administration (see section 5.1, last paragraph).

MedDRA system organ class	Number of AEs									
Preferred term	2006		2007		2008		Total per SAE		Total per SOC	
	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV
Investigations									0	6
alanine aminotransferase increased*		1						1		
aspartate aminotransferase increased*		1						1		
blood alkaline phosphatase increased*		1						1		
C-reactive protein increased*		2						2		
γ-glutamyltransferase increased*		1						1		
Cardiac disorders									0	1
ventricular extrasystoles*		1						1		
Blood and lymphatic system disorders									0	3

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MedDRA system organ class / Preferred term	Number of AEs									
	2006		2007		2008		Total per SAE		Total per SOC	
	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV
leukopenia *		2						2		
thrombocytopenia*		1						1		
Nervous system disorders									0	6
diplegia (feeling of paralysis both legs)†						1		1		
dizziness*		1		1		1		3		
headache*				1				1		
hyperaesthesia†						1		1		
Respiratory, thoracic and mediastinal disorders									0	1
respiratory disorder*						1		1		
Gastrointestinal disorders									0	4
dysphagia*						1		1		
nausea*		1		1		1		3		
Skin and subcutaneous tissue disorders									1	4
rash*				2	1	1	1	3		
urticaria*				1				1		
Musculoskeletal and connective tissue disorders									0	4
arthropathy*		1						1		
pain in extremity*		1				2		3		
Injury, poisoning and procedural complications									0	1
inappropriate schedule of drug administration*						1		1		
Vascular disorders									0	1
syncope*				1				1		
General disorders and administration site conditions									4	49
asthenia*	1						1			
body temperature increased		1		1				2		
chills*	1			1		3	1	4		
general physical health deterioration*				1		1		2		
influenza like illness*						1		1		
injected limb mobility decreased*		1				1		2		
injection site erythema*		1				4		5		
injection site induration*		1						1		
injection site infection*						1		1		
injection site joint pain*		1						1		
injection site pain	1	3				2	1	5		
injection site reaction*		1		2				3		
injection site swelling		1				3		4		
injection site vesicles*		1						1		
injection site warmth*						1		1		
malaise						3		3		
massive swelling injected upper arm*						1		1		
pallor*				1				1		
pain*						2		2		
pyrexia	1	2				6	1	8		
suprapubic pain*						1		1		

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MedDRA system organ class	Number of AEs									
Preferred term	2006		2007		2008		Total per SAE		Total per SOC	
	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV	IPV	Td-IPV
Immune system disorders									0	1
dermatitis allergic*		1						1		
Total	4	28	0	13	1	40	5	81	5	81

* unlisted events
† unlisted but possible symptom of (poly)neuropathy, see section 9.1

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. 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 a Td-IPV combination vaccine. The number of Td-IPV reports by one EU MAH is higher than the reports of plain IPV, probably reflecting vaccinee exposure. 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 the MedDRA system organ classes. During this period a total number of 121 SAEs (32 for plain IPV and 89 for the Td-IPV combination) were reported, concerning 27 vaccinees (12 received plain IPV and 14 received the Td-IPV combination; and 1 vaccinee received either plain IPV, the Td-IPV combination or Td alone). For the calculations of the incidence of SAEs, we used the estimated distributed number of doses of 1,686,131 as explained in section 5.1. The calculated SAE incidence is 121 reports in 1,686,131 doses, corresponding to 7.2 per 100,000 doses, or 1.6 patients per 100,000 doses who experience an SAE.

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 in which most SAEs occurred were *General disorders and administration site conditions* (34), *Nervous system disorders* (34), and *Musculoskeletal and connective tissue disorders* (18). In 12 of 27 patients the SAEs were evaluated as possibly related (6 for plain IPV, 6 for the Td-IPV combination). In 15 cases the SAEs were evaluated as unlikely related to the vaccination, or there were insufficient data. 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.

Some of the unlisted SAEs may be considered within the scope of listed events; e.g., the listed event polyneuropathy is defined as a disorder in several peripheral nerves. A large variety of reported neurological events are possible symptoms of polyneuropathy. These are marked with the symbol [†] in Table 5 and Table 6 and also in the line listings. The reported neurological events mainly concerned sensory disorders and all patients except one had recovered at the time of reporting.

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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.

9.1.1 Plain IPV SAEs

2006-0063: A 51-year old female developed Raynaud's disease, acral necrosis, inflammation of finger tips, morphea skin disorder and raised antinuclear antibody with an unknown latency after vaccination with plain IPV and Td-vaccine separately. The symptoms are progredient. There is insufficient data to assess a causal relationship with the vaccinations. It might be noted that no reports containing comparable events were received.

2006-0345: In a 58-year old male, polyarthritis and increased CRP were reported 9 days after vaccination with IPV and simultaneous administration of oral typhoid vaccine. The patient had not recovered 8 months later, indicating possible lasting damage as seriousness criterion. Arthritis has been reported once before after administration of IPV in 2003, in a 37-year old male and with a latency of 14 days. Vaccine-derived aetiology seems unlikely and with 2 cases reported in about 13 million sold doses in the past 12 years (see Table 7), the reporting rate is very low.

2006-0710: A 42-year old male patient experienced Guillain-Barré syndrome (GBS) 7 weeks after vaccination with either IPV, Td-IPV or Td vaccine, resulting in persisting hand muscle atrophy. In previous years, GBS after IPV administration has been reported once before, in 2002 (see PSUR of 2001-2005). Since 1997, roughly 13 million doses of IPV were sold. In a recent epidemiology review (McGrogan, 2009), the background incidence of GBS is estimated between 1.1/100,000/year and 1.8/100,000/year. Although the cause of GBS is unclear, an antecedent infection less than 4 weeks prior to onset of GBS is reported in 40-70% of GBS patients. Sometimes also vaccines are blamed to be the cause of GBS. In the case of IPV however, the reported incidence of GBS is 2 in roughly 13 million sold doses in 12 years (see Table 7), thus being far below the background incidence.

2006-1019: A 7-month old girl experienced one isolated convulsion 2 days after being vaccinated with IPV. The girl had a medical history of being severely mentally handicapped with autistic signs. The interval between vaccination and onset of the event, and the medical history of the patient make a causal relationship unlikely.

2007-0115: A 58-year old female patient developed an acute pancreatitis 16 days after IPV, and 9 days after Td administration. She was recovering within a couple of weeks. A causal relationship seems unlikely.

2008-0080, 2008-0081, 2008-0082, 2008-0083, 2008-0084: Five IPV SAEs occurred in 6-year old children, 3 females and 2 males. In all 5 cases, injection site erythema was reported, 2 of which also reported injection site pain. The 2 remaining reports also included fever, and either injection site pain or headache. The seriousness criterion was medically significant. It is unclear why these cases were regarded as medically significant. Usually these kinds of adverse events are mild. No additional information is available, and therefore the arguments for seriousness remain unclear. Local pain and fever are listed adverse effects. Local redness is not listed, but is a well-known adverse effect after administration of an injectable vaccine. Headache is also not listed in the SPC, but may reflect a malaise kind of symptom in patients with fever.

2008-0694: A 43-year old male patient experienced an abducent nerve paralysis, 6 days after receiving IPV, and with a hepatitis A and hepatitis B combination vaccine. Approximately 2 weeks before the vaccination he had an upper respiratory tract infection. Additional information on possible differential diagnosis and other causes is lacking.

2008-1088: A premature babygirl was vaccinated with IPV, with DTPw-Hib vaccine and with 7-valent pneumococcal vaccine at the age of 60 days. On vaccination day the baby experienced a significant apnoeic episode, fever 39.6°C, and decreased oxygen saturation. After 2 days she had completely recovered. Fever and apnoea are listed in the SPC. Decreased oxygen saturation is often seen during apnoeic episodes.

2008-2885: In a 13-year old female, injection site pain was reported, as well as dizziness, mild pain in throat, headache, precollapse condition and neurovegetative lability. The symptoms, except injection site pain, are most likely related to the procedure, causing a circulatory reaction.

9.1.2 Td-IPV combination SAEs

2006-0142: A 40-year old female who had a booster vaccination with the Td-IPV combination vaccine had severe pain of the injected upper arm and shoulder after 3 days, and another 3 days later showed signs of muscular weakness. The patient had done physical overwork the weekend before vaccination. Previous vaccination was well tolerated. Injection site pain is expected, though in this case the pain was experienced in the upper arm and shoulder. The physical overwork may very well have contributed to the pain.

2006-0250: A 42-year old male patient developed tingling of tongue and right sided peripheral facial paralysis one hour after receiving his first dose of the Td-IPV combination vaccine. The vaccine was administered subcutaneously into the left side, though the anatomic location was not reported. The patient had fully recovered after 5 weeks. The short latency period makes a causal relationship with the vaccine unlikely.

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2006-0788: A 14-year old female was vaccinated with a first dose of the Td-IPV combination vaccine. The following day she complained about nausea, pain over whole body (especially head and neck), subjective dyspnoea, furry hands and lower thigh, hot feeling, decreased blood pressure and increased pulse rate and she was hospitalised. No further information is available, except that she fully recovered. The symptoms suggest a circulatory reaction (usually related to the injection procedure), headache and some fever.

2006-1109: A 27-year old patient developed pain in the injected arm on the day following vaccination with the Td-IPV combination vaccine. Two days later the mobility of the injected arm decreased and pressure pain in the shoulder joint on the same side developed. After another day there was a neuritis and paresis of the injected arm and she was hospitalised. The patient had not recovered at the time of reporting which was after 6 weeks. The reported symptoms are consistent with polyneuropathy and injection site pain, which are already listed in the SPC.

2007-0048: A 13-year old female developed cough and asthma, 15 days after simultaneous administration of the Td-IPV combination vaccine and a hepatitis B vaccine. It is considered unlikely that the vaccination is related to the occurrence of this event.

2007-0583: A 49-year old male patient received the Td-IPV combination vaccine and a tick-borne encephalitis vaccine. After 13 days he developed after soccer training a severe muscle cramp in his right lower leg. Since then he suffered for months from severe tendency to muscle cramps in both upper and lower legs. Furthermore he suffered from paraesthesia in upper extremities and sleep disorders with unknown latency. Twitching of muscles 4 months later lead to hospitalisation, where restless legs syndrome was diagnosed and fasciculations of both lower legs were seen. Also protrusion of cervical discs 3-6 and thoracic discs 2-3 was diagnosed and eventually treated by surgery. The patient had a slightly depressed mood during the course of disease. The case was reported 3 years later and the patient's condition has improved meanwhile. Except for the paraesthesia, the events are unlisted. It is considered unlikely that the events are related to the vaccination.

2007-0677: A 36 year-old female patient developed fever, arthralgia and a urinary tract infection on the day of vaccination with the Td-IPV combination vaccine. She also complained about nausea and chills. She was hospitalised on the next day and improved under systemic therapy. The fever may have been caused by the vaccination, but also by the urinary tract infection. Chills and nausea are related to the listed events fever and malaise. Arthralgia is an unlisted event. There is no information about the anatomic location of the joint(s) concerned, therefore causality on this event could not be assessed.

2007-0877: A 54-year old male was vaccinated with the Td-IPV combination vaccine and a tick-borne encephalitis vaccine. On the same day the patient showed recurrent fever up to 39°C with chills. On the way to hospital he complained about chest pain with oral dyskinesia and subjective dyspnoea. C-reactive protein was increased, giving a hint to another cause of the symptoms. The fever abated after 3 days and the patient recovered. Medical history included prolapsed disc, condition after myocarditis, recurrent convulsive thoracical complaints and psychovegetative dysregulation. The fever and chills may have been related to the vaccination. The increased C-reactive protein is suggestive for an alternative cause of the symptoms.

2007-1289: (consumer report) A male patient, age unknown, was vaccinated with the Td-IPV combination vaccine inadvertently into the bursa of the shoulder joint. Immediately he developed a long lasting and painful bursitis. The cause of the event is the incorrect administration procedure and not the vaccine itself.

2008-0256: A 62-year old male patient developed swelling at the injection site after vaccination with a first dose of the Td-IPV combination vaccine. On the next day he suffered from neuralgic pain behind the right ear, of head radiating up to throat. He also developed swallowing and chewing pain. Some days later he developed hearing loss of right ear and a peripheral Nervus VII paresis right and was hospitalised for clarification. CSF cell count and total protein (liquor) were increased. Other examinations revealed no pathological findings. The symptoms may indicate polyneuropathy which is a listed event.

2008-1008: A 22-year old female experienced paraesthesia and hypoesthesia of the left face within hours of vaccination with the Td-IPV combination vaccine. She also experienced neck pain in connection with breathing, hyperreflexia and chest discomfort. She was hospitalised on the same day and furthermore suffered from facial pain, fever, and sweaty hands. No additional information on lab tests or examinations is available. Some symptoms may indicate polyneuropathy which is a listed event. Previous vaccination with the Td-IPV combination vaccine was tolerated well.

2008-1032: A 23-year old female received a booster vaccination with the Td-IPV combination vaccine. Approximately one week later the patient was hospitalised, due to tingling paraesthesia of hands and speech disorder and headache (in connection with a 2 weeks before diagnosed migraine with aura). After initial improvement the symptoms occurred again with psychomotoric agitation and amnesia. A moderate liquor pleocytosis and a moderate blood brain barrier defect were found. The treating physician concluded that the symptoms were most likely attributable to a vaccination-associated meningoencephalitis. The disease episode coincides with the recent diagnosis of migraine with aura, and apart from the paraesthesia of hands (which may be a neuropathy symptom), the symptoms are not mentioned in other reports. It is considered unlikely that the events are related to the vaccination.

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2008-1885 (consumer report, medically confirmed): A 56-year old male experienced fever, night sweat, weakness, headache, pain in limbs and joint pain (shoulders and arms) 3 weeks after a fourth dose of the Td-IPV combination vaccine. He was hospitalised one week later. C-reactive protein and leukocyte count were slightly increased. After ineffective treatment with antibiotics the patient recovered soon after cortisone therapy. Medical history included coronary heart disease, hypertensive heart disease, tachyarrhythmia absoluta and allergy to sulphonamide. The interval and the duration of symptoms are both too long for a vaccination reaction to be likely. A virus aetiology is more likely, but because of the lack of any serology tests this hypothesis cannot be confirmed.

2008-2084: A 20-year old female received several vaccinations: the Td-IPV combination vaccine, 11 months later an influenza vaccine, and another 3 months later a hepatitis B vaccine. Two months after the influenza vaccination, the patient suffered from a severe influenza. After the last vaccination, the patient developed fatigue, concentration difficulties, coordination disorder, visual disturbances, disorientation, dizziness and vertigo. Approximately one month later she was hospitalised due to headaches, concentration difficulties, and vertigo. After a number of examinations and hospital episodes, the diagnosis ADEM (Acute Disseminated Encephalomyelitis) was made. The interval of 14 months between Td-IPV vaccination and onset of symptoms is considered too long to suggest causality.

9.2 Reported non-serious adverse events

9.2.1 Listed Non-serious Adverse Events

During the AP, 31 reports containing 81 AEs were received. The incidence of non-serious AEs is low (81 events in 31 cases in 1,686,131 doses).

Table 6 shows that 49 of 81 reported AEs are in the MedDRA SOC "*General disorders and injection site reactions*". Among the listed AEs are injection site reactions (24). The reporting rate would fall in the MedDRA category "very rare". The current MedDRA category is "rare". Since it is expected that there is a huge extent of underreporting there is no need to downgrade the MedDRA category.

There is a variety of descriptions of injection site reactions, not all of which are listed. This is further discussed in section 9.2.2.

Furthermore, the following systemic listed reactions are reported: fever or elevated body temperature (10) sometimes accompanied with chills (4), malaise (3) or comparable symptoms (general physical health deterioration, 2, asthenia, 1, influenza-like illness, 1).

9.2.2 Unlisted Non-serious Adverse Events

The most frequent injection site reaction that is unlisted is redness. It is reported 5 times after use of the Td-IPV combination. Furthermore, there were also 5 SAE reports in which injection site redness was observed after plain IPV administration (reports 2008-0080, 2008-0081, 2008-0082, 2008-0083, 2008-0084). No additional information is available, and therefore the arguments for seriousness remained unclear as is discussed before in section 9.1.1. Considering that injection site reactions are often mild and of short duration, huge underreporting is expected. We propose to update the SPC as follows : "Injection site reactions, such as pain, swelling and redness" instead of "Swelling, pain at the injection site". The MedDRA category 'rare" need not be changed since there are no data justifying a different frequency category.

Most other unlisted non-serious AEs were reported only once or twice. Five out of 86 AEs involved plain IPV, whereas the remaining 81 concerned the Td-IPV combination. Some AEs were reported 3 or 4 times : injection site reaction, pain in extremity, dizziness, nausea, and rash, all of which will be briefly discussed. Only in one of these cases the AEs occured after administration of plain IPV (rash), all others after a Td-IPV combination.

- Injection site reactions were not specified but likely related to the vaccination.
- Pain in extremity is possibly related if in the injected arm, but this information is unknown in the reported cases.
- Dizziness and nausea in 2 cases occurred together, one within minutes after administration of the vaccine. These could be signs of imminent fainting. The possibility of fainting is included as a warning in the SPC (see section 4 and Appendix 1). In the other case dizziness and nausea occurred after 4 days, it seems therefore unlikely to be related to the vaccination. A case with dizziness and malaise with an unknown interval after vaccination could not be judged on causality. In another case nausea occurred after 2 days, also general physical health deterioration, injection site redness, swelling, (all after 2 days) and injection site infection (after 3 days) were reported. It cannot be excluded that it was related to the vaccination.
- Rash was reported four times. In two cases the rash occurred after 1 day and was located either around the mouth (Td-IPV) or in the face and throat (plain IPV). It cannot be excluded that these cases may have been mild allergic reactions. In one other case rash was observed after 2 days in axillary skin folds. A relation with the vaccination seems unlikely. One other case reported rash after two days without information about the anatomic location and distribution. In this case causality could not be assessed.

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Concludingly, there is no reason for any concern about the safety of IPV. As discussed above, one sofar unlisted AE is proposed to be added to the SPC: injection site erythema.

Details of all non-serious AEs can be found in the line listing in Appendix 2.

9.3 Increased reported frequency

Based on the number of sold doses and the number of reported events, there is an apparent increase in the frequency of SAEs, as shown in Table 7. Its significance however should be put into perspective. In previous PSURs only (S)AEs concerning plain IPV were considered, whereas now also SAEs after the administration of a Td-IPV combination were included (as explained in section 5.1, last paragraph). Furthermore the absolute number of reports is very low. Variations in such relatively small numbers of reports could represent chance variation over the years as well as changes in physician awareness of reporting a possible reaction. We think it is reasonable to conclude that the observed apparent increase in frequency of any (S)AE reported during the AP, as compared to previous experience with IPV, is of little importance.

Table 7 Reported frequencies of SAEs

Period	Number of sold doses	Number of reports with AEs (SAEs)	Per 100,000 sold doses:	
			Number of patients with SAE(s)	Number of SAEs
1997-2000	6,164,531	66 (21)	0.34	0.34
2001-2005	5,489,738	22 (22)	0.4	1.11
2006-2008	1,686,131*	57 (27)	1.6	7.2

* This is the number of doses sold used for the calculation of the (S)AE incidence rate. See for explanation paragraph 9.1, page 25.

9.4 Other safety issues

Drug interactions

No suspected drug interactions were reported during the AP.

Overdose

During the AP no reports describing overdosing of IPV were received.

Drug abuse or misuse

During the AP one report of an incorrect route of administration was reported by a consumer. The report was not medically confirmed. The Td-IPV combination vaccine was injected intrabursal instead of intramuscular. The patient suffered from a long-lasting and painful bursitis. The cause of the bursitis should be seen in the incorrect route of vaccine administration and not in the vaccine itself.

Furthermore, one report was received of an inappropriate administration schedule of 2 doses within 4 weeks, the result of which may be an inadequate immune response.

Use in Pregnancy and Lactation

No reports on the use of IPV during pregnancy or lactation were received during the AP.

Use in Special Patient Groups

Plain IPV is in some countries, but not in The Netherlands, used as part of immunisation programmes for infants and children. It is also used for the immunisation of adults. Most reports involved adults, which could represent a

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difference of vaccinee exposure to IPV. The low reporting rate in general hampers a meaningful comparison between the different age groups. No special patient groups could be identified that indicate a safety concern for the use of IPV.

Effect of long-term treatment

Not applicable.