AGENDA ITEM NUMBER 11 *PAPER NUMBER JCVI (09)22*

JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

TITLE OF PAPER

Vaccine safety report from MHRA

REASON FOR INCLUSION

- For discussion

ACTION REQUIRED BY THE COMMITTEE

- To note

LIST OF PAPERS/ARTICLES ATTACHED	**Publication status**
• MHRA, 2009 – Vaccine-associated suspected adverse reactions reported via the yellow card scheme during 2008.	JCVI website

Paper provided by MHRA for
Joint Committee on Vaccination and Immunisation
June 2009:

VACCINE-ASSOCIATED SUSPECTED ADVERSE REACTIONS REPORTED VIA THE YELLOW CARD SCHEME DURING 2008

June 2009

CONTENTS

Introduction

This paper was prepared by Medicines and Healthcare products Regulatory Agency (MHRA) for the June 2009 Meeting of the Joint Committee of Vaccination and Immunisation (JCVI).

Section 1 of this paper provides an update on UK suspected adverse reactions (ADRs) associated with routine and/or commonly used vaccines reported to the MHRA/CHM via the Yellow Card Scheme during the time period of 1st January 2008 to 31st December 2008.

Precise vaccine exposure data for 2008 were not available at the time of writing this report. For specific vaccines, such as particular routine childhood vaccines, an uptake percentage has been assumed; however it has not been possible to make any assumptions for the remaining vaccines. As a result estimated reporting rates for the former are unreliable and for the latter have not been calculated. As the estimated reporting rates are based on imprecise data and assumptions, no firm conclusions can be drawn on relative rates over time.

Section 2 provides an update on key vaccine safety papers considered by the Commission on Human Medicines (CHM) and/or its Expert Advisory Groups during 2008 and to date.

Prepared; May 2009

Vigilance and Risk Management of Medicines (VRMM)
Medicines and Healthcare products Regulatory Agency

1. YELLOW CARD DATA

It should be noted that a report of a suspected adverse drug reaction (ADR) to the MHRA/CHM does not necessarily mean that it has been caused by the vaccine. Many factors have to be taken into account in assessing the relationship between a vaccine and suspected reaction such as the possible role of underlying or undiagnosed illness or infection.

Furthermore, the number of reports received should not be used as a basis for estimating the incidence of ADRs due to variable levels of reporting and as the number of individuals immunised is not always know.

Please note that one Yellow Card may contain more than one serious ADR. Seriousness is determined by regulatory criteria (MedDRA Dictionary serious). Yellow Card data covers the whole of the UK.

1.1 Routine Childhood Vaccines

1.1.1. Menitorix (MenC/Hib combination)

Menitorix was introduced into the routine childhood schedule in September 2006 as a single dose MenC/Hib booster at around 12 months of age. Although this is a novel combination, prior to introduction there was extensive worldwide experience with the similar monocomponent Hib and MenC vaccines conjugated to tetanus toxoid (e.g. Hiberix and Neisvac-C vaccines).

The total number of suspected ADRs reported in association with Menitorix over the last 2 years is shown below (table 1). On the assumption of 90% uptake for an annual birth cohort of 650,000 (one dose), it estimated that 585,000 children received a single dose of Menitorix during 2008.

Table 1: Total number of Menitorix reports received (serious reports in brackets)

	2006	2007	2008
Total number of reports	11 (5)	60 (16)	48 (12)
Total number of reactions	24 (5)	144 (17)	99 (17)
Total fatal	0	0	2
Exposure	200,000	585,000	585,000
ERR per 100,000 doses	5.5 (2.5)	10.3 (2.7)	8.2 (2.1)

ERR = Estimated Reporting Rate

Table 2 lists the serious ADRs reported (note – one Yellow Card may contain more than one serious ADR).

Table 2: Serious ADRs reported for Menitorix (2009)

Serious Suspected ADR		No of reports
Systen Organ Class (SOC)	**Preferred Term (PT)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	LYMPHADENOPATHY	1
CARDIAC DISORDERS	CARDIAC ARREST	1
EYE DISORDERS	EYE OEDEMA	1
INFECTIONS AND INFESTATIONS	ERYTHEMA INDURATUM	1
	BRONCHITIS	1
	OSTEOMYELITIS	1
INVESTIGATIONS	BODY TEMPERATURE FLUCTUATION	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	INCORRECT DOSE ADMINISTERED	1
	WRONG DRUG ADMINISTERED	2
	VACCINATION ERROR	1
	ACCIDENTAL OVERDOSE	1
IMMUNE SYSTEM DISORDERS	ANAPHYLACTIC REACTION	2
NERVOUS SYSTEM DISORDERS	HYPOTONIA	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	PULMONARY OEDEMA	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	SYSTEMIC LUPUS ERYTHEMATOSUS RASH	1

Figure 1 shows the serious ADRs reported in each MedDRA System Organ Class (SOC), as a percentage of the total ADRs, for the last two years. The majority of the serious ADRs reported for Menitorix vaccine in 2008 belonged to the 'Injury, Poisoning and Procedural Complications' SOC, followed by the 'Infections and Infestations' SOC. There has been a marked decrease in the number of ADRs reported in the 'Nervous System Disorders' SOC in comparison to 2007.

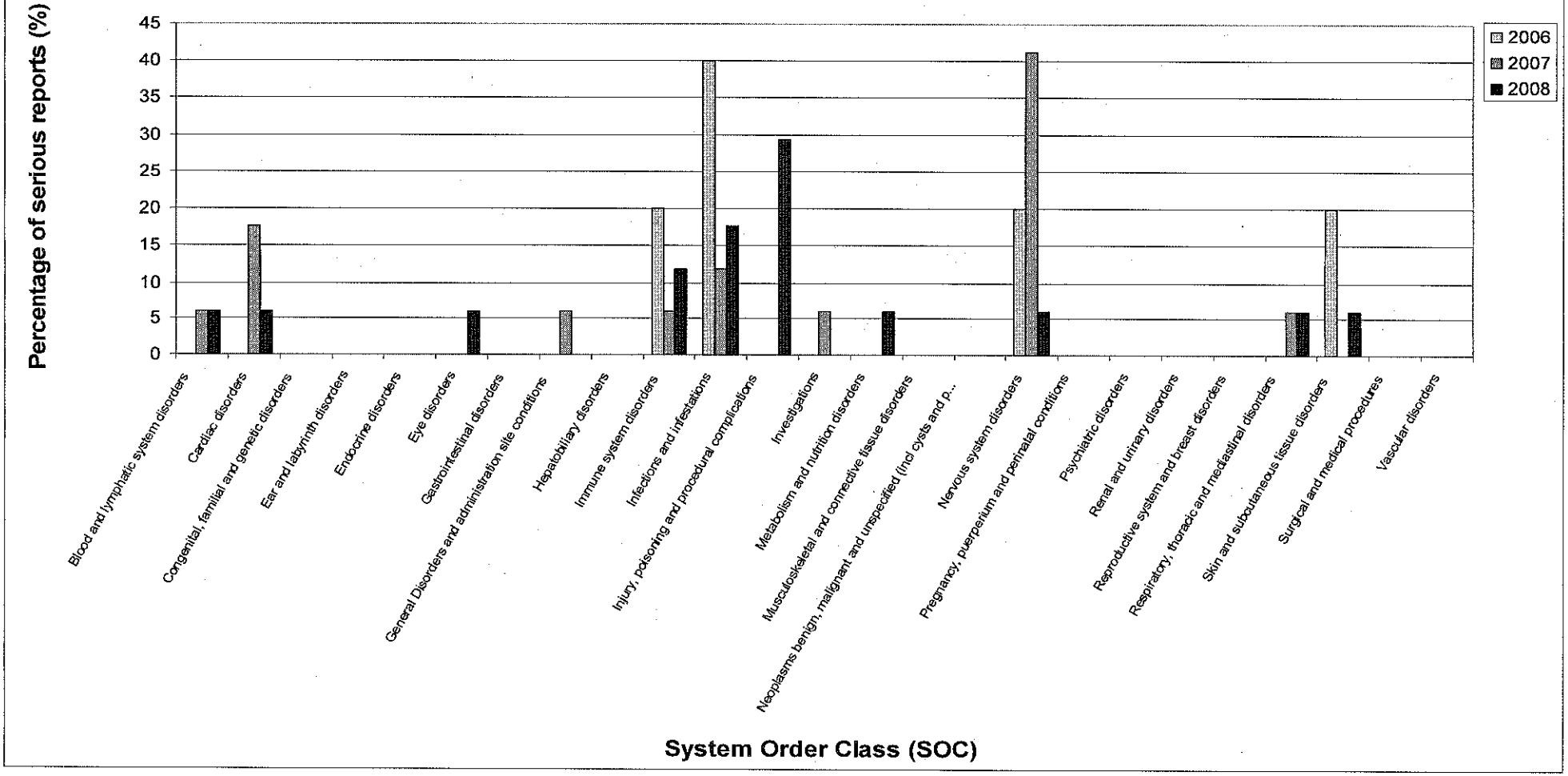
The MHRA is monitoring reports of administration errors which are mainly due to confusion between Menitorix and single constituent Meningitis C vaccine; however the evidence does not suggest that this is due to any packaging issue. This could account for the increased incidence of reports in the 'Injury, Poisoning and Procedural Complications' SOC.

There were two fatal reports of 'Cardiac Arrest' and 'Haemophilus Infection' in 2008; a causal association with these fatal events has not been established.

Overall adverse drug reaction reporting numbers remain very small.

Conclusion: No significant new safety issues were identified during 2008.

Figure 1: Percentage of serious reactions per SOC associated with Menitorix vaccine



1.1.2. Prevenar (pneumococcal conjugate vaccine)

Prevenar was introduced into the routine childhood schedule in September 2006. It is currently recommended for use at 2 months, 4 months and around 13 months of age. Prior to UK introduction, there was substantial international experience in the safety of Prevenar.

The total number of suspected ADRs reported in association with pneumococcal conjugate vaccine over the last 3 years is shown below (table 3).

UTable 3: Total number of Prevenar reports (serious reports in brackets)

	2006	2007	2008
Total number of reports	334 (52)	294 (79)	146 (37)
Total number of reactions	689 (58)	675 (108)	323 (45)
Total fatal	0	2	3
Exposure	1,500,000	1,800,000	1,800,000
ERR per 100,000 doses	22.3 (3.4)	16.3 (4.4)	8.1 (2.1)

ERR = Estimated Reporting Rate

On the assumption of 90% uptake for an annual birth cohort of 650,000 (3 doses), it estimated that 1.8m doses of Prevenar were administered during 2008.

Figure 2 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. The majority of the serious ADRs reported for Prevenar vaccine in 2008 belonged to the 'Nervous System Disorders' SOC, followed by the 'Infections and Infestation' SOC and the 'Respiratory, Thoracic and Mediastinal Disorders' SOC.

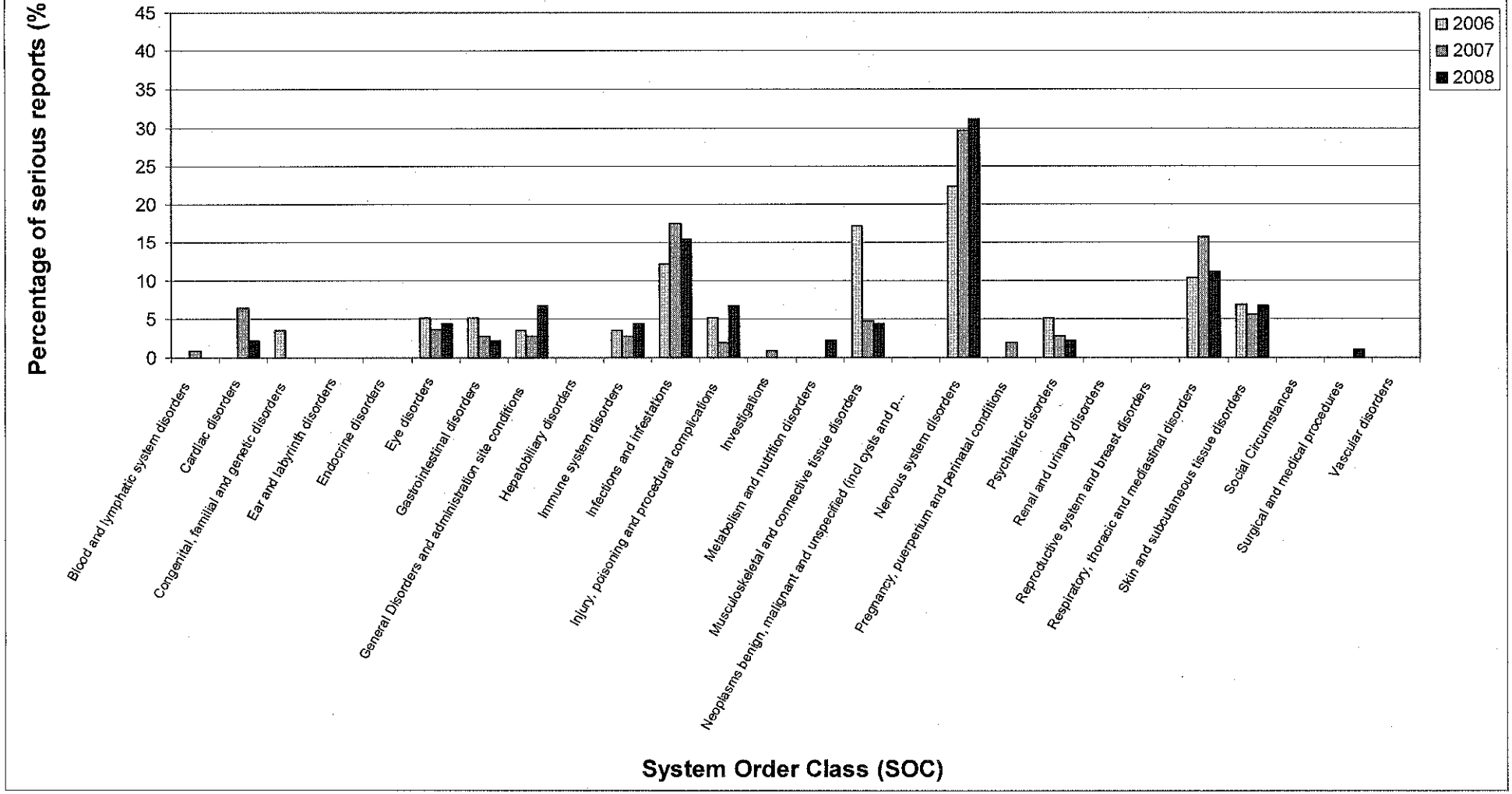
There was an increase in the percentage of serious reactions reported in the 'Nervous system disorders' SOC. The most reported serious reaction from this SOC is 'Hypotonia' (6 cases), followed by 'Convulsion' (2 cases) and 'Febrile Convulsion' (2 cases).

Two fatal reports of sudden infant death syndrome and one fatal report of lung disorder were reported in 2008. A casual association with these fatal events has not been established.

It is notable that overall reporting rates have reduced over time which possibly reflects familiarity with the vaccine.

Conclusion: No significant new safety issues were identified during 2008.

Figure 2: Percentage of serious reactions per SOC associated with Prevenar vaccine



1.1.3. Pediacel and Infanrix IPV Hib (DTPa/IPV/Hib)

The total number of suspected ADRs reported in association with DTPa/IPV/Hib for the last 3 years is shown below (table 4).

Table 4: Total number of DTaP/IPV/Hib vaccine reports and doses distributed (serious reports in brackets)

	2006	2007	2008
Total number of reports	116 (38)	171 (48)	264 (61)
Total number of reactions	254 (49)	403 (67)	581 (81)
Total fatal	1	1	5
Exposure	1,833,000	2,000,000	2,340,000
ERR per 100,000 doses	6.32 (2.1)	8.6 (2.4)	11.3 (2.6)

ERR = Estimated Reporting Rate

The total number of ADRs increased in 2008 compared to 2007 and 2006. This is partly explained by the increased exposure of the vaccine(s) as a pre-school booster from the end of 2007.

A Haemophilus influenzae type B (Hib) vaccine catch-up campaign was started in early September 2007 and ran until March 2009. The use of Repevax (dTaP/IPV) and Infanrix IPV (DTaP/IPV) as pre-school boosters was replaced with Infanrix IPV Hib (DTaP IPV Hib) vaccine (and possibly Pediacel in a few cases). Taking account of the increased exposure as part of the Hib catch-up (pre-school boosters from September 2007), it is estimated that 2,340,000 doses of DTaP/IPV/Hib were administered during 2008 (assuming 90% uptake for an annual birth cohort of 650,000 [x3 doses], plus 650,000x0.9 [1 dose]).

Figure 3 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years.

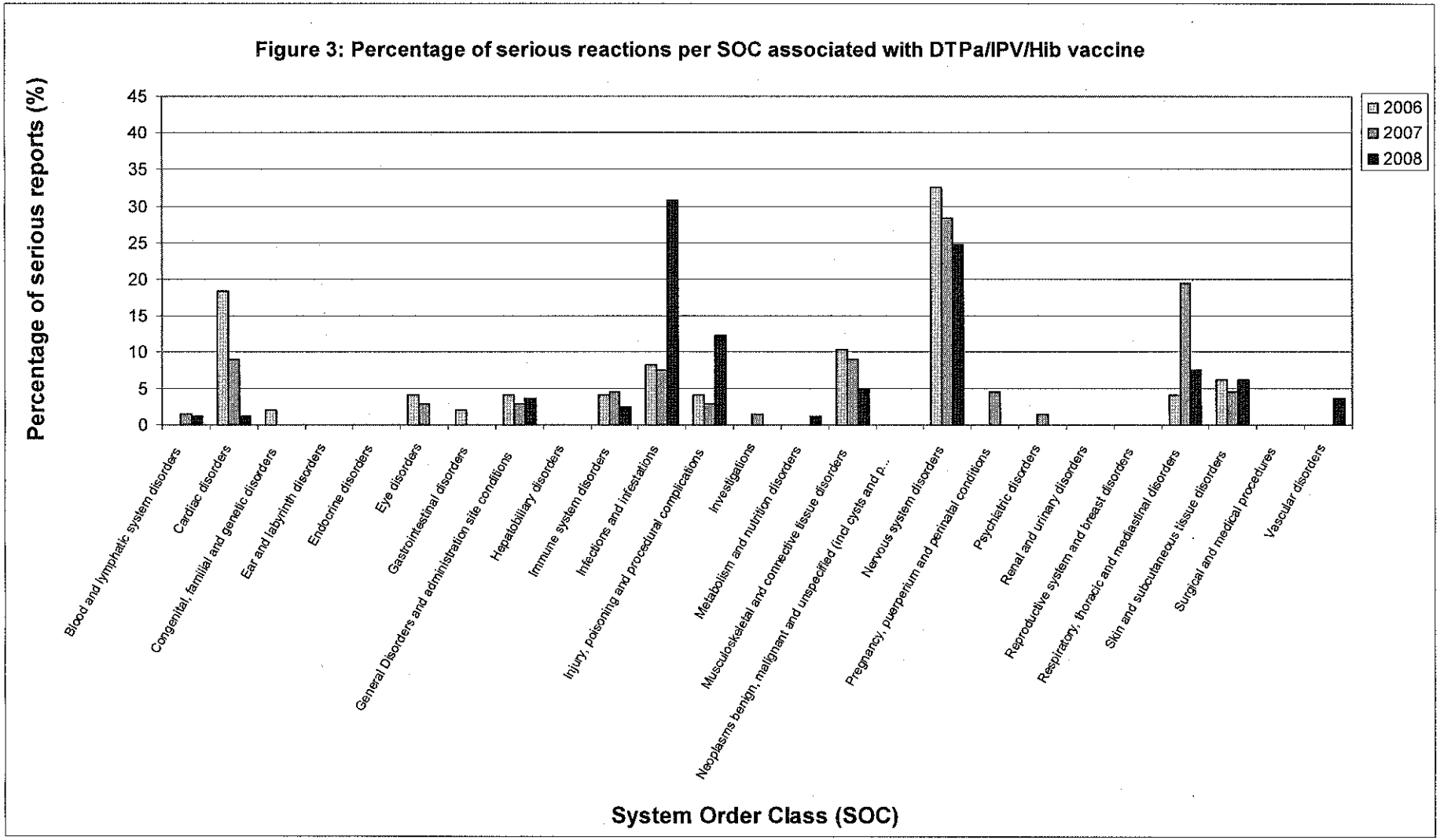
On the whole, the types of serious reactions reported in 2008 were broadly similar to those reported in the previous year. Approximately 25% of serious ADRs were from the 'Nervous System Disorders' SOC and largely consisted of 'Hypotonia' and 'Convulsion' (hypotonic hyporesponsive episodes and convulsions are recognised reactions). There was a decrease in the number of serious ADRs in the 'Respiratory, Thoracic and Mediastinal Disorders' SOC and an increase in the 'Injury, Poisoning and Procedural Complications' SOC.

Approximately 31% of serious reactions reported in 2008 were from the 'Infections and Infestations' SOC, up from 7% in 2007; the most reported serious reaction in this SOC was 'Cellulitis' (13 reactions). These cases were most probably extensive limb swelling, which is a well-recognised phenomenom with a 4th dose of a DTaP vaccine, and the increase probably reflects the fact that this cohort was fully primed with a DTaP vaccine (whereas previous cohorts would have been primed with a DTwP vaccine. There was an increase in percentage of reactions in the 'Injury, Poisoning and Procedural Complications' SOC; these mostly consisted of vaccine complications or failures. This reflects the issue raised in 2008 of administration errors allegedly due to foreign-labelled packs of Infanrix IPV Hib.

Two fatal reports of 'Sudden Infant Death Syndrome', one of 'Pneumococcal Sepsis', one of 'Haemophilus Infection' and one of 'Lung Disorder' were reported in 2008. A casual association with these fatal events has not been established. The case of 'Haemophilus Infection' was mentioned above under Menitorix (Pediacel was co-suspect as the primary vaccine series).

Conclusion: No significant new safety issues were identified during 2008.

Figure 3: Percentage of serious reactions per SOC associated with DTPa/IPV/Hib vaccine



1.1.4. MMR vaccine

The total number of suspected ADRs reported in association with MMR vaccination for the last 3 years is shown below (table 5).

On the assumption of 85% uptake for an annual birth cohort of 650,000 (2 doses), it estimated that 1,105,000 routine doses of MMR were administered during 2008. However, due to ongoing catch-up initiatives, exposure is likely to be much greater than this.

A new MMR vaccine, M-M-R VaxPro (M-M-R II with recombinant albumin), was introduced in December 2008; however up to the end of 2008 no adverse drug reaction reports were received for this vaccine.

UTable 5: Total number of MMR vaccine reports and doses distributed (serious reports in brackets)

	2006	2007	2008
Total number of reports	151 (66)	100 (51)	123 (65)
Total number of reactions	338 (95)	295 (83)	307 (91)
Total fatal	2	2	1
Exposure	1,105,000	1,105,000	1,105,000
ERR per 100,000 doses	13.7 (6.0)	9.0 (4.6)	11.1 (5.9)

ERR = Estimated Reporting Rate

Figure 4 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. Overall, the pattern and type of reactions has not changed with the most reported serious reactions of 'Convulsion' (9 cases) and 'Arthralgia' (6 cases).

The percentage of serious reactions reported in the 'Musculoskeletal and Connective Tissue Disorders' SOC increased to 19% in 2008, compared to 5% in 2007. The most commonly reported reaction in this SOC was 'Arthralgia'.

There was also an increase in percentage of serious reactions in the 'Gastrointestinal Disorders' SOC; these reactions consisted of 'Lip Swelling' (5 cases), 'Swollen Tongue' (3 cases) and one case of 'Oedema Mouth'.

There was one fatal report of myocarditis reported during 2008. A causal association with this fatal event has not been established.

Conclusion: No significant new safety issues were identified during 2008.

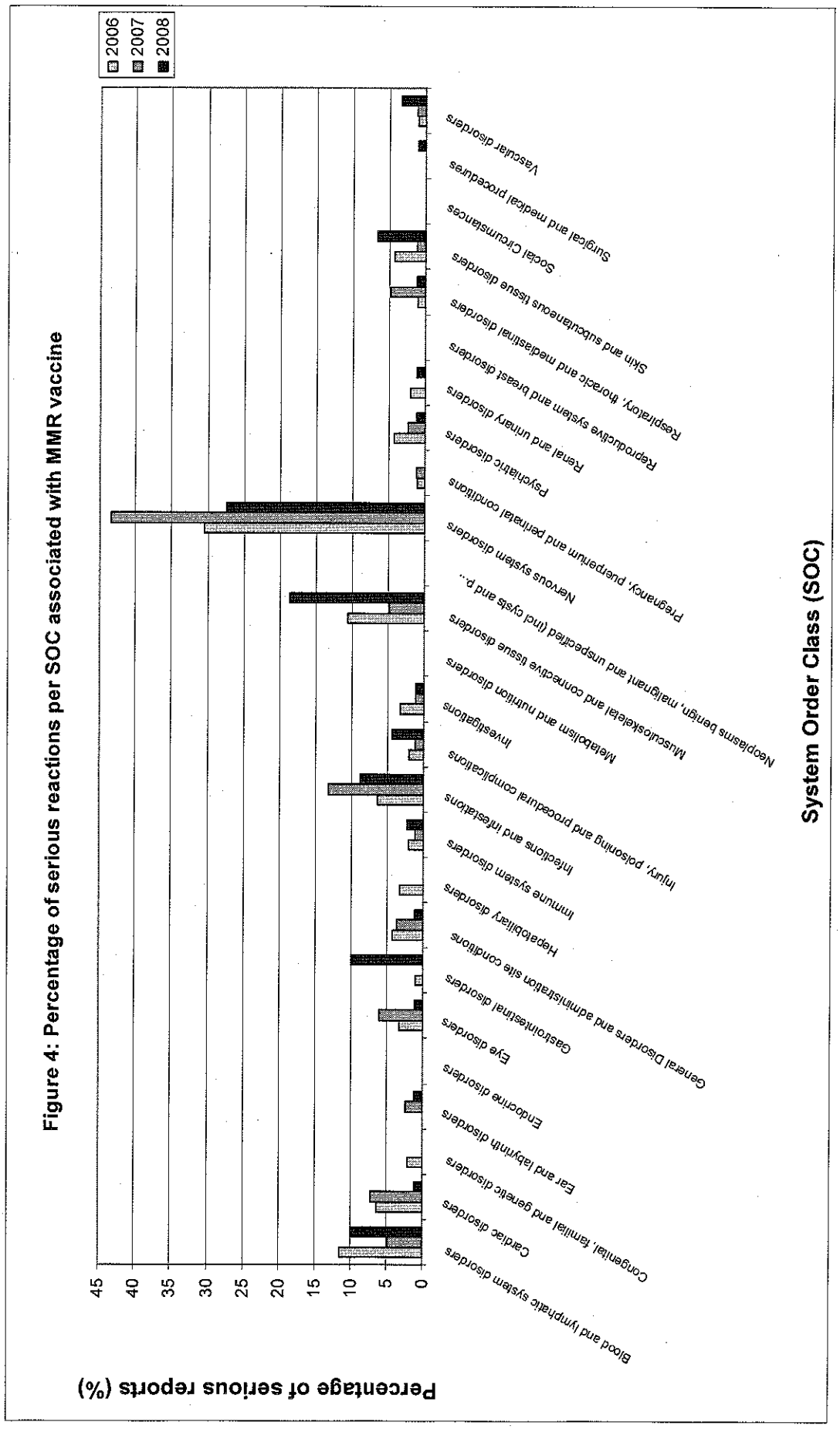


Figure 4: Percentage of serious reactions per SOC associated with MMR vaccine
2006
2007
2008
Percentage of serious reports (%)
0
5
10
15
20
25
30
35
40
45
Blood and lymphatic system disorders
Cardiac disorders
Congenital, familial and genetic disorders
Ear and labyrinth disorders
Endocrine disorders
Eye disorders
Gastrointestinal disorders
General Disorders and administration site conditions
Hepatobiliary disorders
Immune system disorders
Infections and infestations
Injury, poisoning and procedural complications
Investigations
Metabolism and nutrition disorders
Musculoskeletal and connective tissue disorders
Neoplasms benign, malignant and unspecified (incl cysts and p...
Nervous system disorders
Pregnancy, puerperium and perinatal conditions
Psychiatric disorders
Renal and urinary disorders
Reproductive system and breast disorders
Respiratory, thoracic and mediastinal disorders
Skin and subcutaneous tissue disorders
Social Circumstances
Surgical and medical procedures
Vascular disorders
System Order Class (SOC)

1.1.5. Meningitis C vaccine

The total number of suspected ADRs reported in association with Meningococcal group C conjugate vaccine for the last 3 years is shown below (table 6).

Table 6: Total number of Meningitis C vaccine reports and doses distributed (serious reports in brackets)

	2006	2007	2008
Total number of reports	72 (24)	65 (20)	54 (16)
Total number of reactions	179 (37)	141 (30)	120 (28)
Total fatal	1	0	2
Exposure	1,630,000	1,170,000	1,170,000
ERR per 100,000 doses	4.4 (1.5)	5.6 (1.7)	4.6 (1.4)

ERR = Estimated Reporting Rate

On the assumption of 90% uptake for an annual birth cohort of 650,000 (2 doses), it estimated that 1.17m doses of Menigitis C conjugate vaccines were administered during 2008.

Figure 5 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last 3 years. The SOC with the largest proportion of serious reactions was the 'Nervous System Disorders' SOC, with the most reported serious reaction in this SOC being 'Hypotonia' (2 cases). There was one case of suspected vaccination failure reported in literature.

There were 2 fatal reports during 2008, one case of 'Lung Disorder' and one case of 'Histiocytosis Haematophagic'. A casual association with these fatal events has not been established.

Conclusion: No significant new safety issues were identified during 2008.

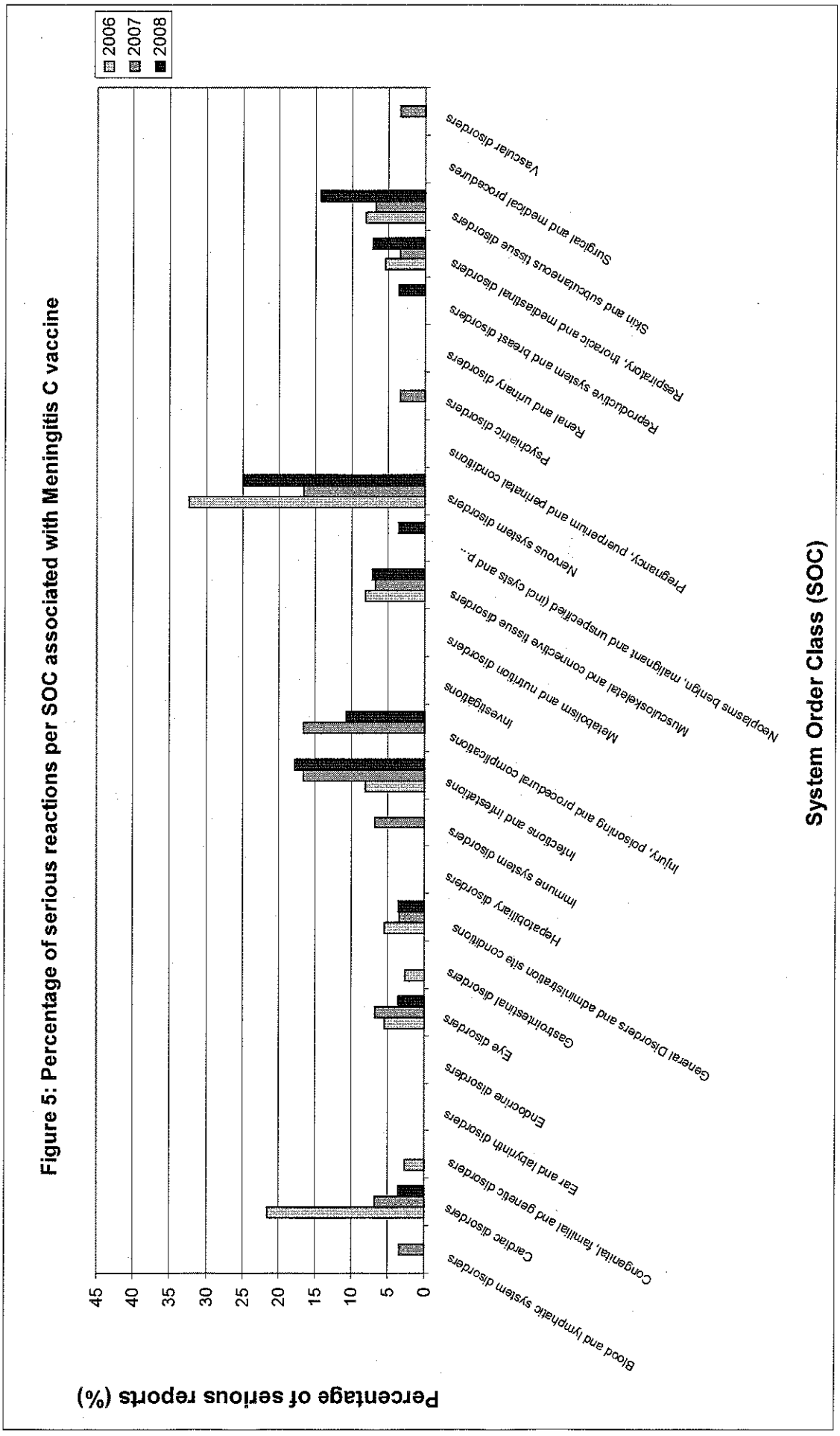


Figure 5: Percentage of serious reactions per SOC associated with Meningitis C vaccine

1.1.6. Repevax/Infanrix IPV (d/DTaP/IPV)

The total number of suspected ADRs reported in association with d/DTaP/IPV vaccine for the last 3 years is shown below (table 7). The total number of reports reported for d/DTaP/IPV vaccine has fallen steadily since 2006.

Table 7: Total number of reports and doses distributed (serious reports in brackets)

	2006	2007	2008
Total number of reports	207 (43)	71 (14)	9 (1)
Total number of reactions	423 (48)	161 (15)	20 (1)
Total fatal	0	0	0
Exposure	611,000	440,000	n/a
ERR per 100,000 doses	33.9 (7.0)	16.1 (3.2)	n/a

ERR = Estimated Reporting Rate

The exposure rate for Repevax and Infanrix IPV have not been calculated as these vaccines were not routinely used in 2008 due to the HIB catch-up campaign.

Figure 6 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last 3 years. There was just one serious suspected reaction of 'Syncope' reported in 2008.

There have been no suspected ADRs with a fatal outcome associated with this vaccine since its launch in 2004.

Conclusion: No significant new safety issues have been identified during 2008.

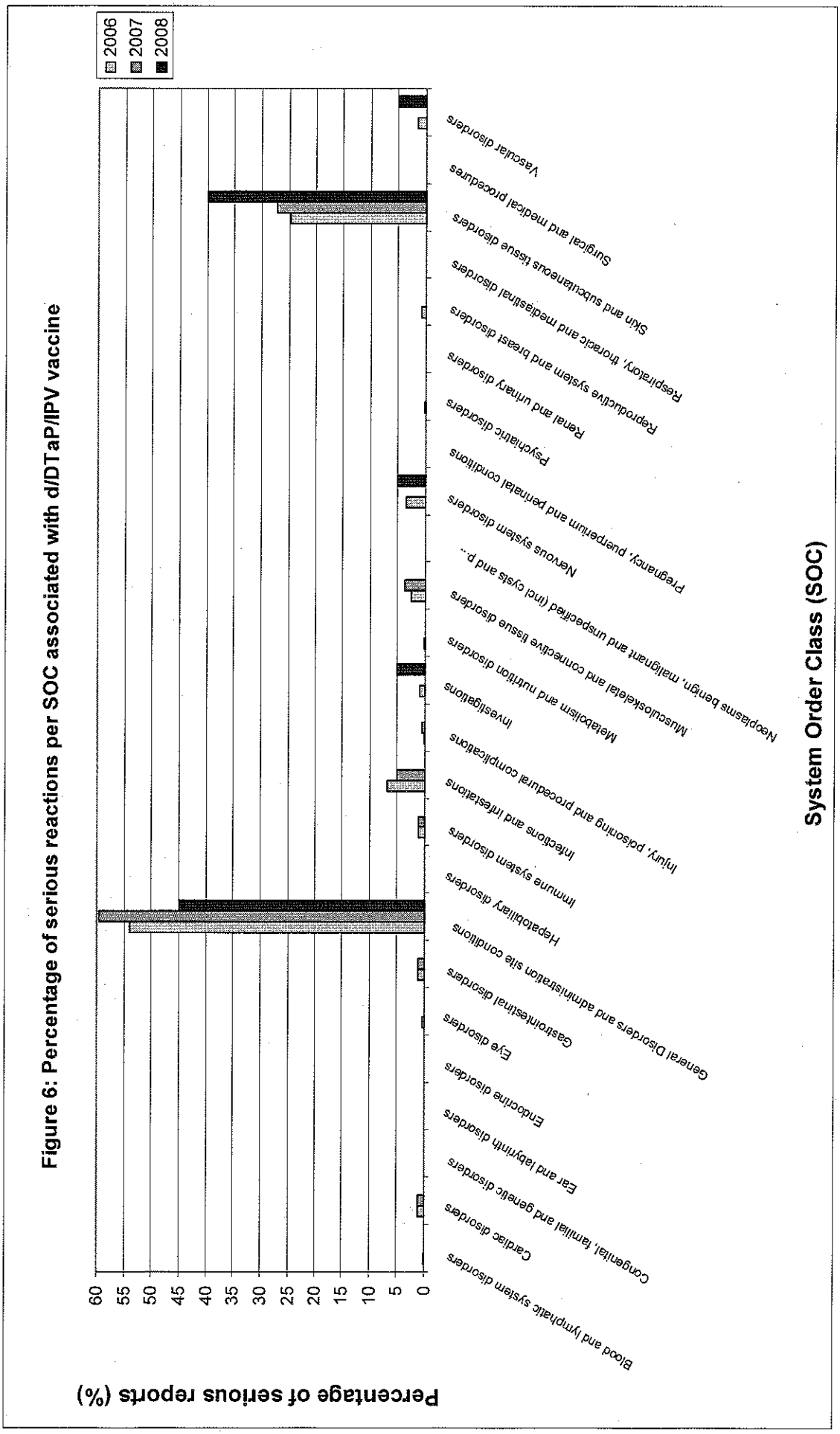


Figure 6: Percentage of serious reactions per SOC associated with d/DTaP/IPV vaccine
2006
2007
2008
Percentage of serious reports (%)
60
55
50
45
40
35
30
25
20
15
10
5
0
Blood and lymphatic system disorders
Cardiac disorders
Congenital, familial and genetic disorders
Ear and labyrinth disorders
Endocrine disorders
Eye disorders
Gastrointestinal disorders
General Disorders and administration site conditions
Hepatobiliary disorders
Immune system disorders
Infections and infestations
Injury, poisoning and procedural complications
Investigations
Metabolism and nutrition disorders
Musculoskeletal and connective tissue disorders
Neoplasms benign, malignant and unspecified (incl cysts and p...
Nervous system disorders
Pregnancy, puerperium and perinatal conditions
Psychiatric disorders
Renal and urinary disorders
Reproductive system and breast disorders
Respiratory, thoracic and mediastinal disorders
Skin and subcutaneous tissue disorders
Surgical and medical procedures
Vascular disorders
System Order Class (SOC)

1.1.7. Revaxis (dT/IPV)

Revaxis is a booster vaccine given to young people aged between 13 and 18 as well as for adult boosters. The total number of suspected ADRs reported in association with dT/IPV vaccine for the last 3 years is shown below (table 8).

Table 8: Total number of Revaxis reports and doses distributed (serious reports in brackets)

	2006	2007	2008
Total number of reports	81 (30)	107 (39)	83 (44)
Total number of reactions	217 (39)	313 (67)	257 (73)
Total fatal	0	1	2
Exposure	n/a	n/a	n/a
ERR per 100,000 doses	n/a	n/a	n/a

ERR = Estimated Reporting Rate
n/a: Data not available at the time of writing this report.

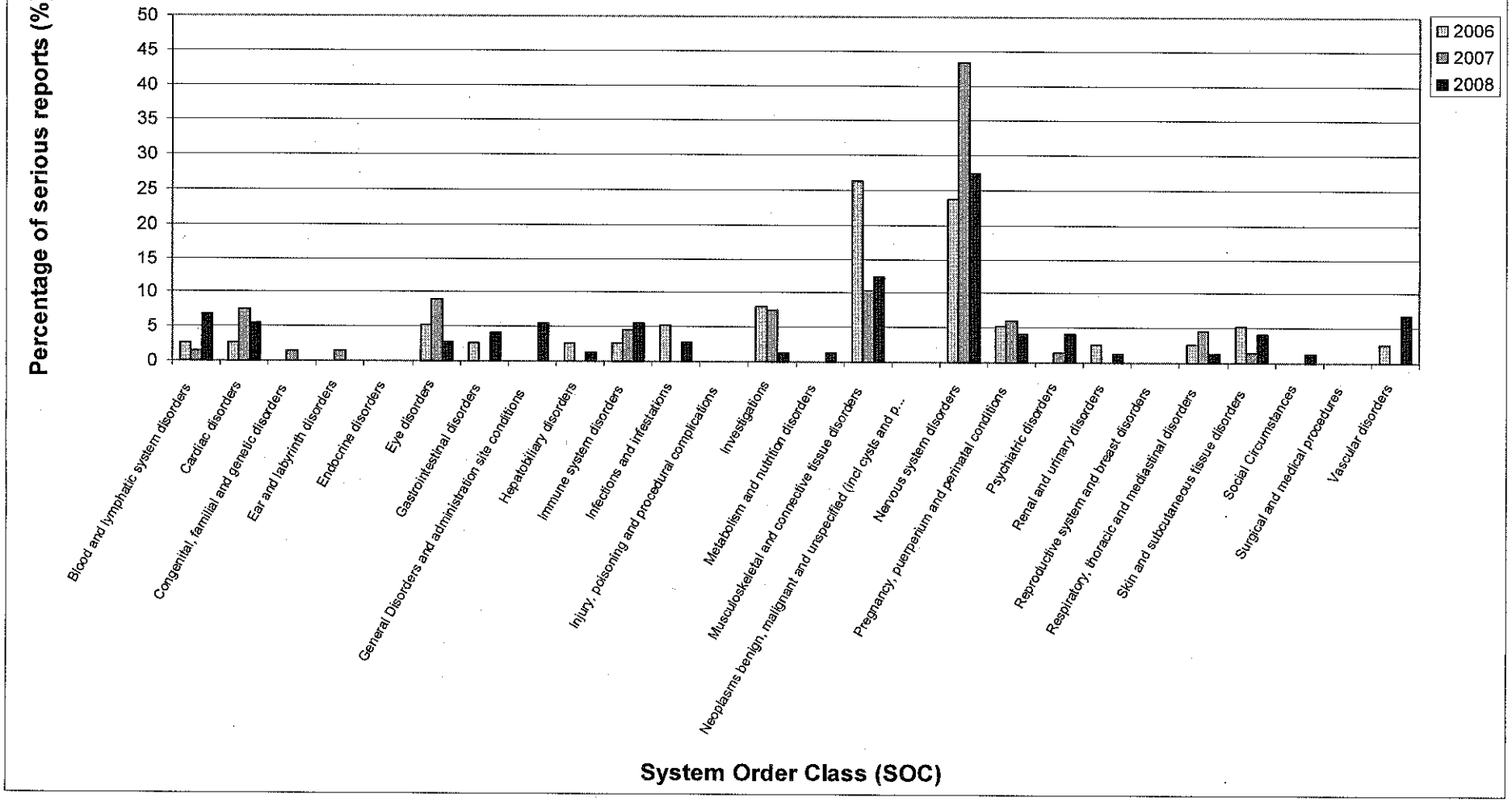
The total number of ADRs reported has decreased by 24 reports for 2008 compared to 2007. The distribution data for the vaccine during 2008 were not available at the time of writing this report and as such, ERRs have not been calculated.

Figure 7 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. The majority of serious reactions are within the nervous system disorders SOC with 8 reports of syncope.

There were two fatal reports associated with this vaccine in 2008. One fatal report was of 'Cerebral Haemorrhage' and one of 'Pneumococcal Sepsis'. A casual association with the fatal event was not established.

Conclusion: No significant new safety issues have been identified during 2008.

Figure 7: Percentage of serious reactions per SOC associated with Revaxis vaccine



1.2 New vaccines

1.2.1. Gardasil▼ and Cervarix▼ (Human Papillomavirus) vaccine

Gardasil was first authorised in September 2006 and Cervarix in November 2007. Cervarix vaccine was introduced to the UK routine immunisation schedule in September 2008. This was offered to all girls aged 12-13 years to protect them against the risk of cervical cancer. There is also an additional catch-up campaign for girls aged up to 18 years. The timing of catch-programmes may differ in Scotland, Wales and Northern Ireland. Three doses of the vaccine are required at 0, 1, and 6 months, respectively, to offer protection against HPV types 16 and 18.

The total number of suspected ADRs reported in association with Gardasil vaccines over the last 2 years is shown below (table 9). Gardasil and Cervarix are new UK vaccines and have Black Triangle status (requiring all suspected ADRs to be reported). Gardasil is not being used as part of the national HPV immunisation programme but is available on prescription. Low number of suspected ADRs during 2007 and 2008 is in line expectations due to low uptake in comparison to Cervarix.

Table 9: Total number of Gardasil vaccine reports received (serious reports in brackets)

	2007	2008
Total number of reports	1	23
Total number of reactions	2 (1)	55 (14)
Total fatal	0	0
Exposure	n/a	n/a
ERR per 100,000 doses	n/a	n/a

ERR = Estimated Reporting Rate
n/a: Data not available at the time of writing this report.

Since the introduction of the national HPV immunisation programme, approximately 500,000 doses of Cervarix has been administered in the UK up to the end of December 2008.

Three possible issues of concern have been identified from the safety experience of Cervarix vaccine in the UK – Facial palsy, Guillain Barre Syndrome (GBS) and Chronic Fatigue Syndrome (CFS). More details regarding these issues and the current safety experience of the national HPV programme are provided in Section 2.2.

Conclusion: Other than Facial palsy, GBS and CFS, no significant new safety issues have been identified during 2008.

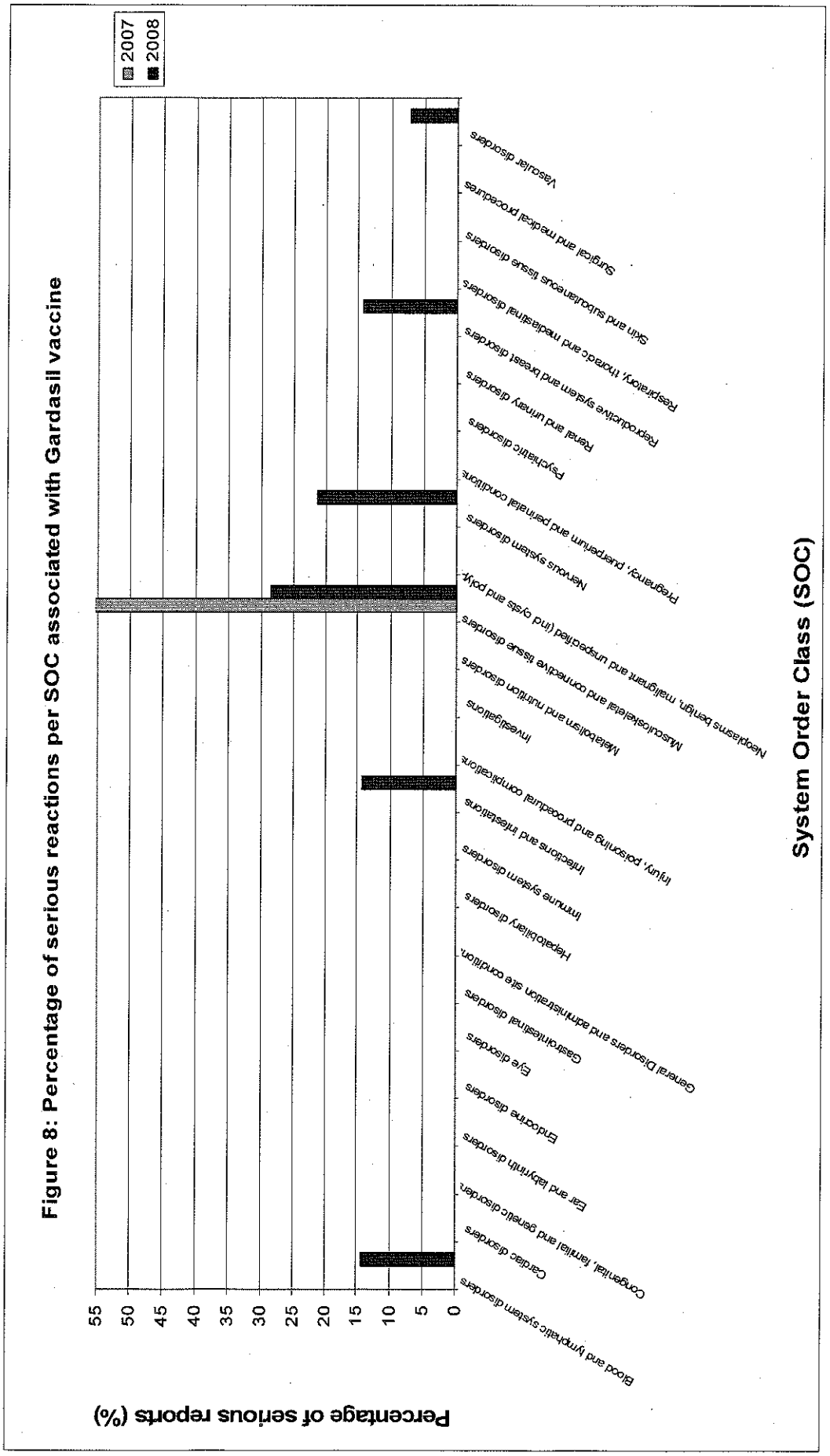


Figure 8: Percentage of serious reactions per SOC associated with Gardasil vaccine
2007
2008
Percentage of serious reports (%)
55
50
45
40
35
30
25
20
15
10
5
0
Blood and lymphatic system disorders
Cardiac disorders
Congenital, familial and genetic disorder
Ear and labyrinth disorders
Endocrine disorders
Eye disorders
Gastrointestinal disorders
General Disorders and administration site condition
Hepatobiliary disorders
Immune system disorders
Infections and infestations
Injury, poisoning and procedural complication
Investigations
Metabolism and nutrition disorders
Musculoskeletal and connective tissue disorders
Neoplasms benign, malignant and unspecified (incl cysts and polyp
Nervous system disorders
Pregnancy, puerperium and perinatal conditions
Psychiatric disorders
Renal and urinary disorders
Reproductive system and breast disorders
Respiratory, thoracic and mediastinal disorders
Skin and subcutaneous tissue disorders
Surgical and medical procedures
Vascular disorders
System Order Class (SOC)

1.3 Other vaccines

1.3.1. Hepatitis B vaccine

The total number of suspected ADRs reported in association with single hepatitis B vaccine for the last 3 years is shown below (table 10).

Table 10: Total number of Hepatitis B vaccine reports and doses distributed (serious reports in brackets)

	2006	2007	2008
Total number of reports	116 (66)	131 (58)	105 (69)
Total number of reactions	413 (105)	359 (93)	396 (133)
Total fatal	0	0	2
Exposure	n/a	n/a	n/a
ERR per 100,000 doses	n/a	n/a	n/a

ERR = Estimated Reporting Rate
n/a: Data not available at the time of writing this report.

The distribution data for the vaccine during 2008 were not available at the time of writing this report and as such, ERRs have not been calculated.

Figure 9 shows the serious ADRs reported in each SOC, as a percentage of the total serious ADRs, for the last three years. The majority of serious reactions occurred within the 'Musculoskeletal and connective tissue disorders' SOC and the 'Nervous System Disorders' SOC. The most reported serious reaction in each of these two SOCs is 'Arthralgia' (10 cases) and 'Syncope' (13 cases).

There were two fatal reports associated with this vaccine in 2008. One fatal report was of congenital herpes simplex infection and one of encephalitis. A casual association with these fatal events has not been established.

Conclusion: No significant new safety issues have been identified during 2008.

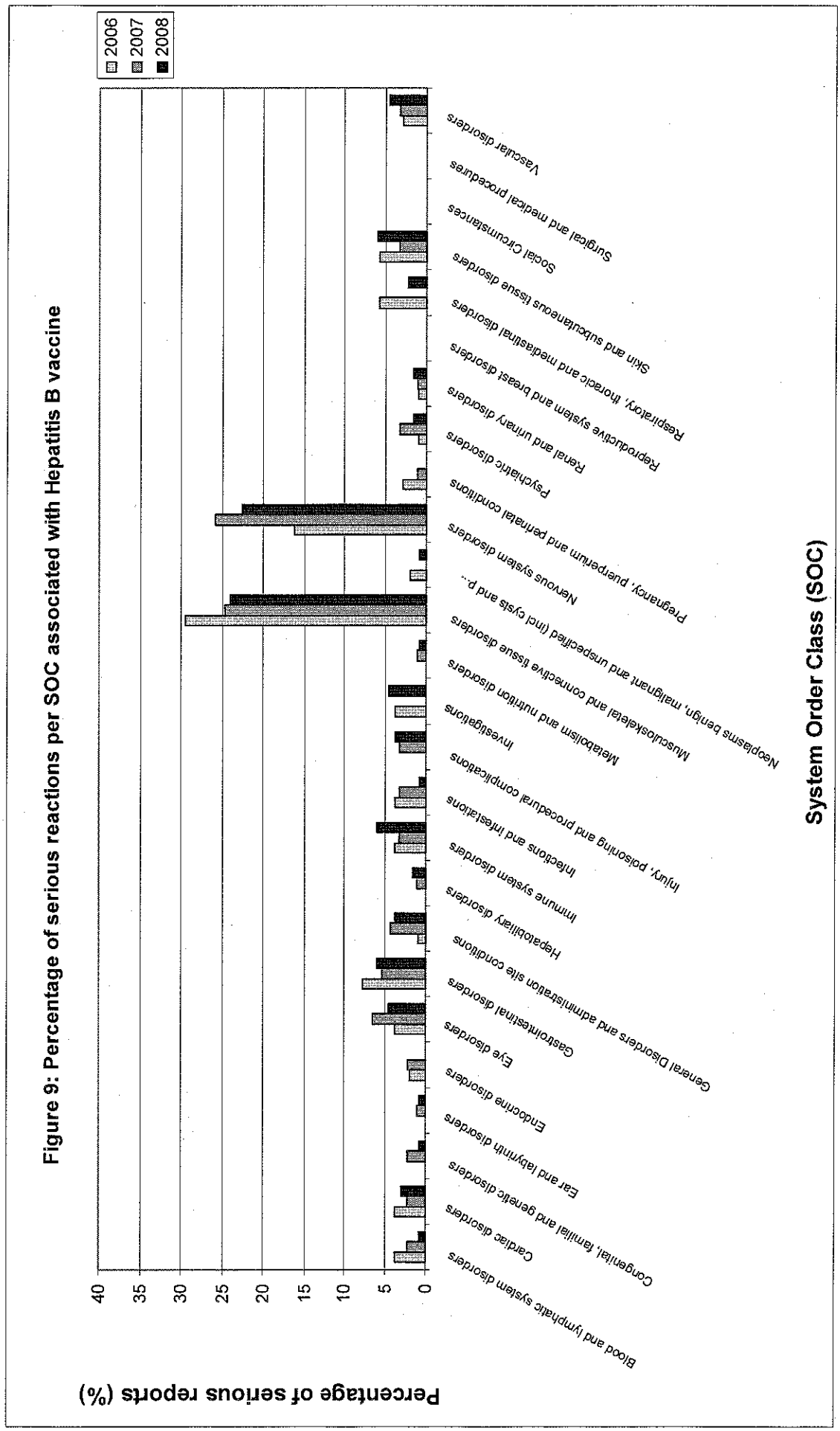


Figure 9: Percentage of serious reactions per SOC associated with Hepatitis B vaccine
Percentage of serious reports (%)
2006
2007
2008
0
5
10
15
20
25
30
35
40
Blood and lymphatic system disorders
Cardiac disorders
Congenital, familial and genetic disorders
Ear and labyrinth disorders
Endocrine disorders
Eye disorders
Gastrointestinal disorders
General Disorders and administration site conditions
Hepatobiliary disorders
Immune system disorders
Infections and infestations
Injury, poisoning and procedural complications
Investigations
Metabolism and nutrition disorders
Musculoskeletal and connective tissue disorders
Neoplasms benign, malignant and unspecified (incl cysts and p...
Nervous system disorders
Pregnancy, puerperium and perinatal conditions
Psychiatric disorders
Renal and urinary disorders
Reproductive system and breast disorders
Respiratory, thoracic and mediastinal disorders
Skin and subcutaneous tissue disorders
Social Circumstances
Surgical and medical procedures
Vascular disorders
System Order Class (SOC)

1.3.2. Influenza vaccine

The total number of suspected ADRs reported in association with influenza vaccine for the last 3 years is shown below (table 11). The number of reports received over this period has maintained relatively constant.

Table 11: Total number of Influenza reports and doses distributed (serious reports in brackets)

	2006	2007	2008
Total number of reports	130 (77)	115 (62)	113 (62)
Total number of reactions	400 (130)	302 (98)	310 (105)
Total fatal	3	5	5
Exposure	14,000,000	14,000,000	14,000,000
ERR per 100,000 doses	0.9 (0.6)	0.8 (0.4)	0.8 (0.4)

ERR = Estimated Reporting Rate

As in previous years, exposure has been estimated at 14m doses.

Figure 10 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. The majority of serious reactions occurred within the 'Musculoskeletal and Connective Tissue Disorders' SOC and the 'Nervous System Disorders' SOC. The most reported serious reactions in the 'Musculoskeletal and Connective Tissue Disorders' SOC were 'Arthralgia' (5 cases) and 'Myalgia' (5 cases), and in the 'Nervous System Disorders' SOC was 'Guillain-Barre Syndrome' (4 cases) [the available epidemiological evidence does not support a causal association between current seasonal flu vaccines and GBS].

There were five suspected ADRs with a fatal outcome in 2008. There was one case of death unexplained, one of 'Myocardial Infarction', one of 'Anaphylactic Shock' and one of 'Histiocytosis Haematophagic'. There was also a fatal report of 'Drug Toxicity'; however this refers to carbamazepine toxicity, with influenza vaccine being a co-suspect drug. In view of the patient population and in the context of the numbers of doses administered, this does not give rise to concern.

Conclusion: No significant new safety issues have been identified during 2008.

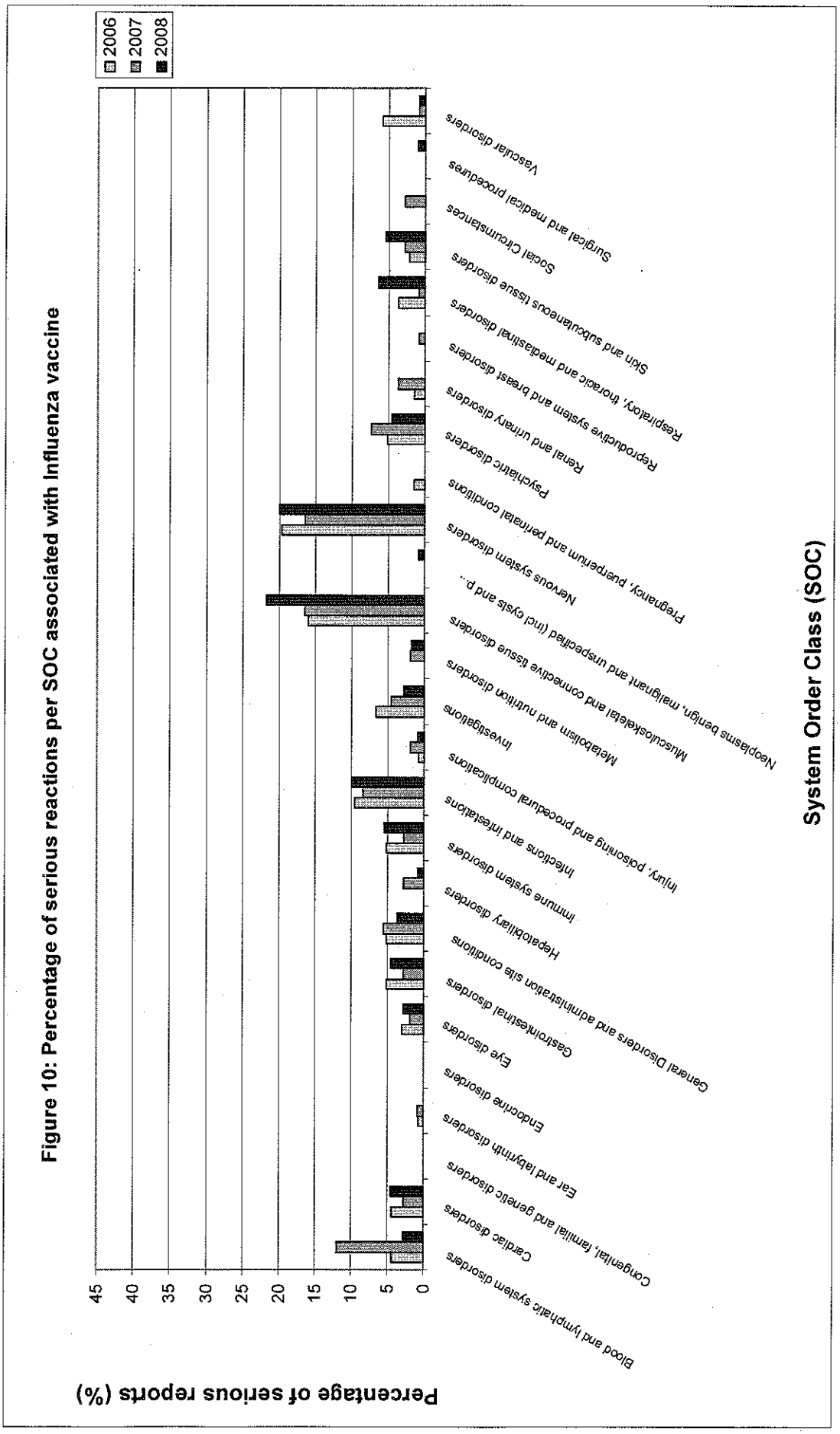


Figure 10: Percentage of serious reactions per SOC associated with Influenza vaccine
2006
2007
2008
Percentage of serious reports (%)
0
5
10
15
20
25
30
35
40
45
Blood and lymphatic system disorders
Cardiac disorders
Congenital, familial and genetic disorders
Ear and labyrinth disorders
Endocrine disorders
Eye disorders
Gastrointestinal disorders
General Disorders and administration site conditions
Hepatobiliary disorders
Immune system disorders
Infections and infestations
Injury, poisoning and procedural complications
Investigations
Metabolism and nutrition disorders
Musculoskeletal and connective tissue disorders
Neoplasms benign, malignant and unspecified (incl cysts and p...
Nervous system disorders
Pregnancy, puerperium and perinatal conditions
Psychiatric disorders
Renal and urinary disorders
Reproductive system and breast disorders
Respiratory, thoracic and mediastinal disorders
Skin and subcutaneous tissue disorders
Social Circumstances
Surgical and medical procedures
Vascular disorders
System Order Class (SOC)

1.3.3. Pneumococcal polysaccharide vaccine

The total number of suspected ADRs reported in association with pneumococcal polysaccharide vaccine for the last 3 years is shown below (table 13).

Table 13: Total number of Pneumococcal polysaccharide vaccine reports and doses distributed (serious reports in brackets)

	2006	2007	2008
Total number of reports	129 (58)	92 (49)	89 (26)
Total number of reactions	394 (87)	284 (51)	252 (50)
Total fatal	1	0	3
Exposure	n/a	n/a	n/a
ERR per 100,000 doses	n/a	n/a	n/a

ERR = Estimated Reporting Rate
n/a: Data not available at the time of writing this report.

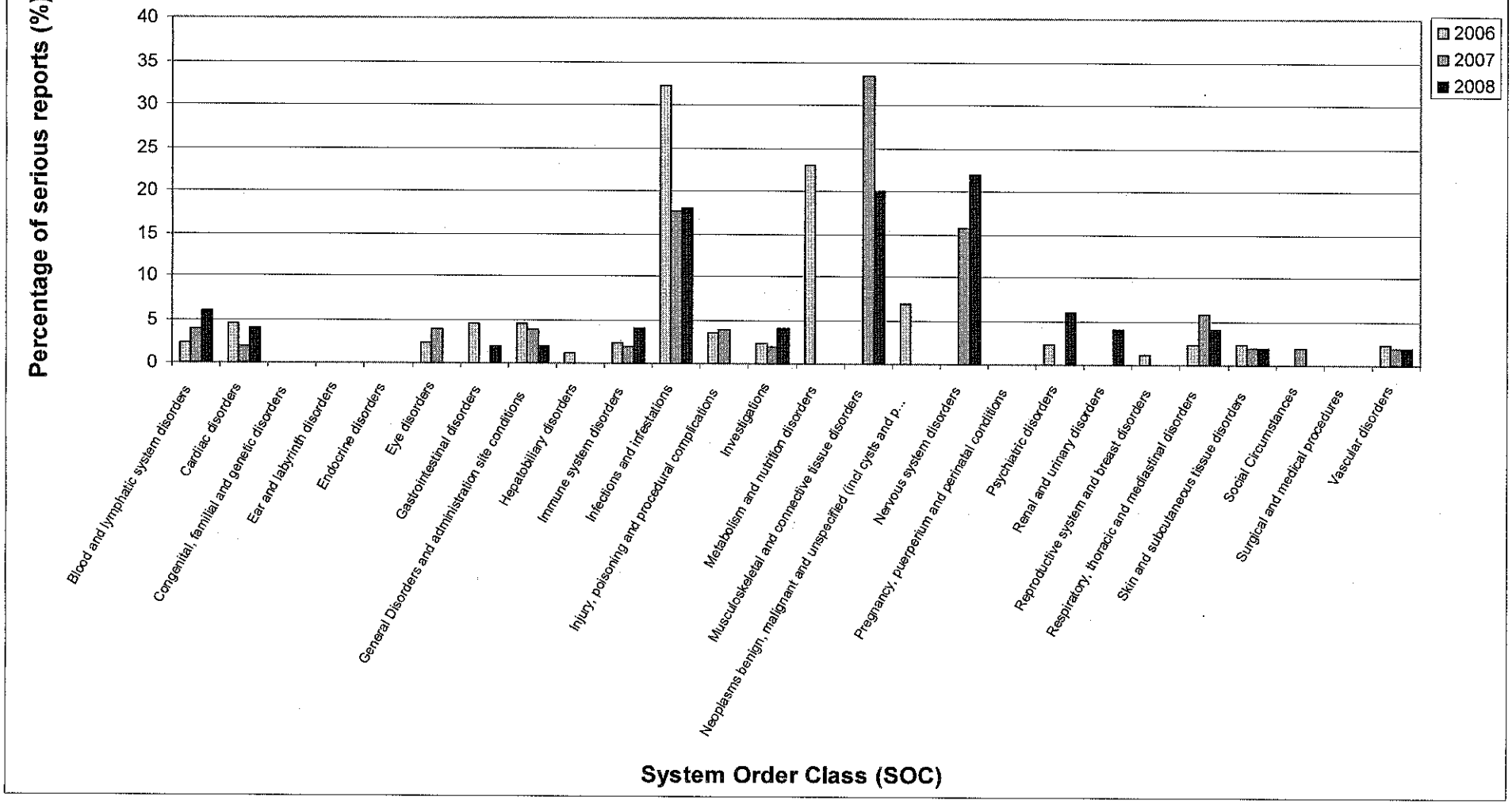
The distribution data for the vaccine during 2008 were not available at the time of writing this report and as such, ERRs have not been calculated.

Figure 10 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. The majority of serious reactions occurred within the 'Musculoskeletal and Connective Tissue Disorders' SOC and the 'Nervous System Disorders' SOC. The most reported serious reaction in each of these two SOCs is 'Arthralgia' (3 cases) and 'Syncope' (2 cases), which are recognised reactions.
There were also a large proportion of reactions within the 'Infections and Infestations' SOC; the most reported serious reaction in this SOC was 'Cellulitis' (4 cases), which is a recognised reaction.

There were three suspected ADRs with a fatal outcome in 2008. There was one case of 'Anaphylactic Reaction', one case of 'Cardiac Disorder' and one case of 'Immune System Disorder'. In view of the patient population and in the context of the numbers of doses administered, this does not give rise to concern.

Conclusion: No significant new safety issues have been identified during 2008.

Figure 11: Percentage of serious reactions per SOC associated with Pneumococcal Polysaccharide vaccine



1.3.4. BCG vaccine

The total number of suspected ADRs reported in association with BCG vaccine for the last 3 years is shown below (table 14).

Table 14: Total number of BCG reports and doses distributed (serious reports in brackets)

	2006	2007	2008
Total number of reports	38 (11)	40 (22)	110 (13)
Total number of reactions	46 (11)	64 (24)	49 (16)
Total fatal	1	0	0
Exposure	n/a	n/a	n/a
ERR per 100,000 doses	n/a	n/a	n/a

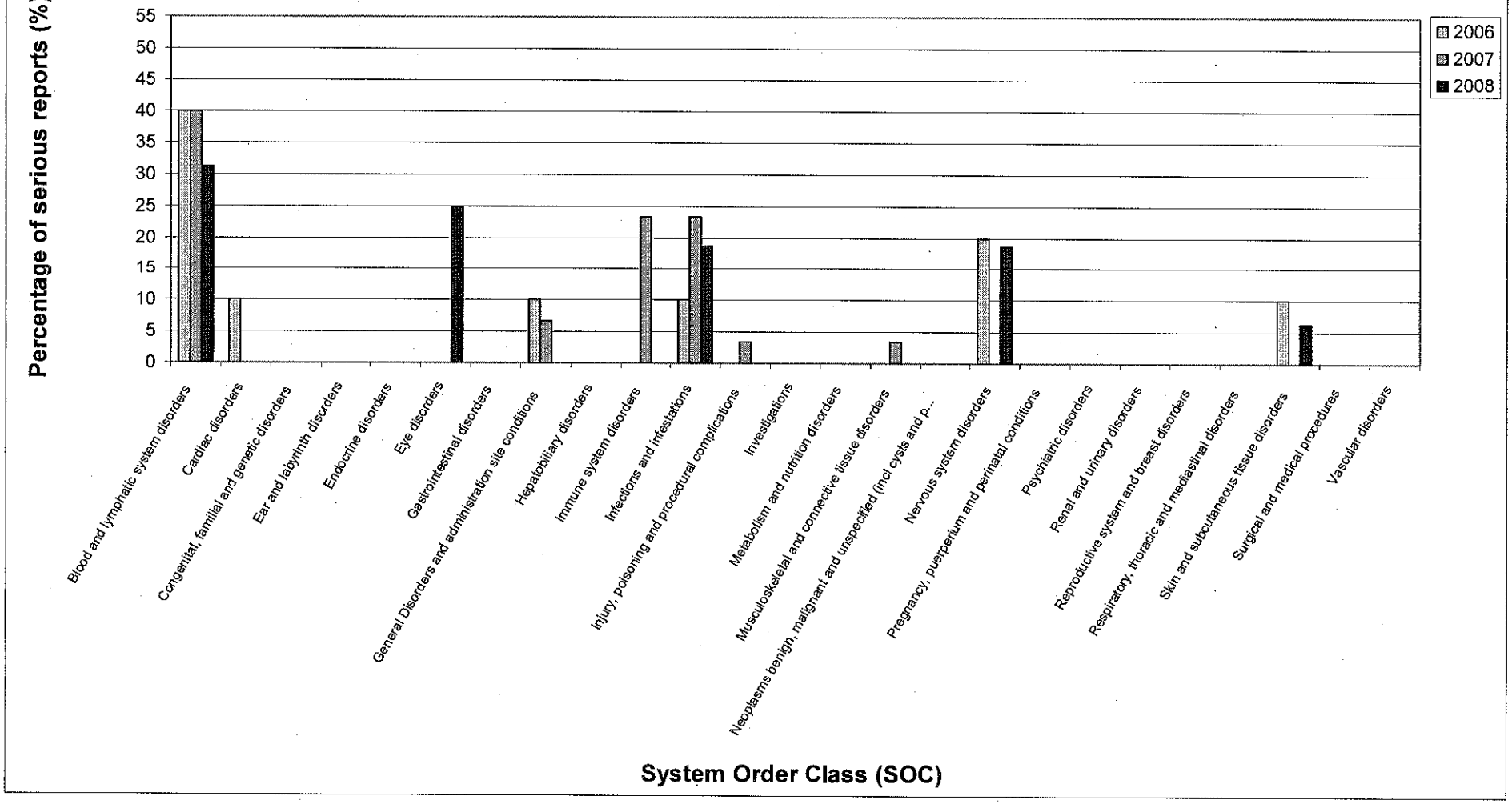
ERR = Estimated Reporting Rate
n/a: Data not available at the time of writing this report.

The distribution data for the vaccine during 2008 were not available at the time of writing this report and as such, ERRs have not been calculated.

Figure 12 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. The majority of serious reactions occurred within the 'Blood and Lymphatic System Disorders' SOC and 'Eye Disorders' SOC. The most reported reactions in the 'Blood and Lymphatic System Disorders' SOC were 'Lymphadenitis' and 'Lymphadenopathy' (both of which are recognised reactions). There were two cases of 'Uveitis', one case of 'Ocular Hyperaemia' and one case of 'Visual Acuity Reduced' for the 'Eye Disorders' SOC. There was 1 report of 'Tuberculosis' reported during 2008.

Conclusion: No significant new safety issues have been identified during 2008.

Figure 12: Percentage of serious reactions per SOC associated with BCG vaccine



1.3.5. Varivax▼ and Varilrix▼ (Varicella Zoster Virus) vaccines

Varivax was first authorised in January 2004 and Varilrix was first authorised in June 2002. The total number of suspected ADRs reported in association with varicella zoster virus for the last 3 years is shown below (table 15).

Table 15: Total number of Varicella zoster vaccine reports (serious reports in brackets)

	2006	2007	2008
Total number of reports	19 (9)	24 (16)	19 (11)
Total number of reactions	66 (17)	62 (25)	49 (24)
Total fatal	1	0	0
Exposure	n/a	n/a	n/a
ERR per 100,000 doses	n/a	n/a	n/a

ERR = Estimated Reporting Rate
n/a: Data not available at the time of writing this report.

The distribution data for the vaccine during 2008 were not available at the time of writing this report and as such, ERRs have not been calculated.

The table below (Table 16) lists the serious ADRs reported in 2008 (note – one Yellow Card may contain more than one serious ADR). Seriousness is determined either by regulatory criteria or by reporter judgement.

Table 16: Serious reactions reported for Varicella Zoster Virus

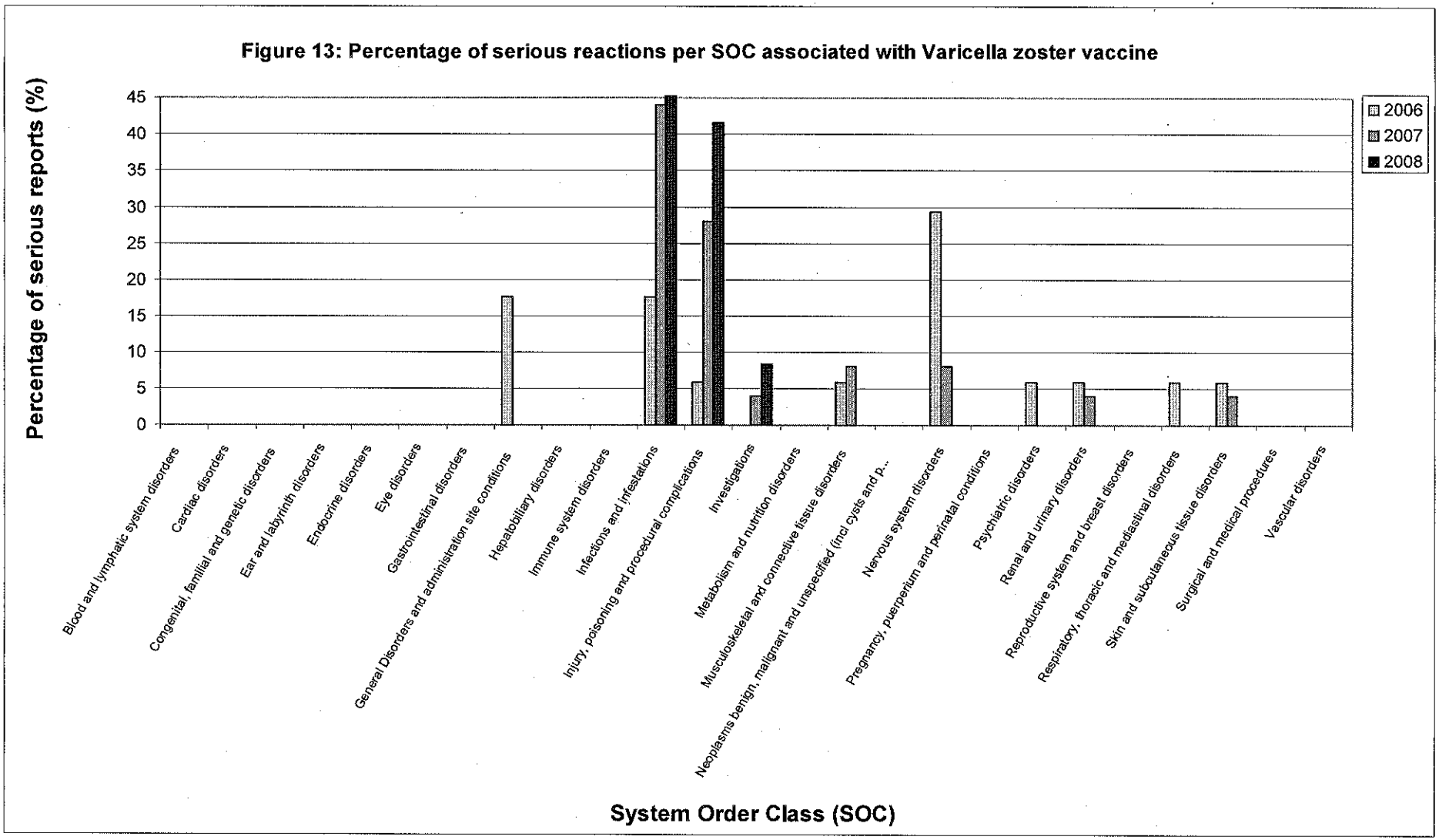
Reaction (PT)	Number of Reports
VACCINATION FAILURE	10
VARICELLA	11
VARICELLA POST VACCINE	1
BLOOD PRESSURE INCREASED	1
HEART RATE IRREGULAR	1

The majority of serious reactions occurred within the 'Injury, poisoning and procedural complications' SOC and 'Infections and infestations' SOC. These were mainly vaccination failure (10 cases) and varicella (11 cases). Figure 13 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years.

In relation to vaccine failures, the Summaries of Product Characteristics (SPCs) for Varivax and Varilirix have been updated this year to include a two-dose schedule in order to provide long-term protection.

Conclusion: No significant new safety issues have been identified during 2008.

Figure 13: Percentage of serious reactions per SOC associated with Varicella zoster vaccine



2. SECTION 2: ISSUES CONSIDERED BY THE COMMISSION ON HUMAN MEDICINES (CHM) AND/OR ITS EXPERT ADVISORY GROUPS DURING 2008 AND TO DATE

2.1 Update on Rotateq vaccine and Intussusception and Kawasaki's disease

RotaTeq and Rotarix are both authorised within the EU but only RotaTeq is currently approved in the US. Within Europe, the UK is rapporteur for RotaTeq and therefore directly responsible for monitoring its ongoing safety; Belgium is the rapporteur for Rotarix.

Because of previous experience with Rotashield, pre-licensing studies were designed to identify an increased risk of intussusception. Whilst neither study identified an increase in risk, that for RotaTeq could not exclude a 6-fold increase and that for Rotarix could not exclude a 4-fold increase.

Since the approval of these vaccines in Europe Kawasaki Disease was been identified as a potential in association with RotaTeq but has not been confirmed. Large post-marketing surveillance studies are seeking to further investigate a possible association with both intussusception and Kawasaki Disease. To date no signals have been identified on the basis of interim analyses.

We are not aware of any safety concerns with respect to Rotarix; however, Rotarix has so far been used in countries whose Pharmacovigilance systems are likely to be less well developed than the US and Europe.

2.2 Human Papillomavirus (HPV) vaccine – Safety Experience with the National HPV Immunisation Programme

Since the start of the national HPV programme, at least 800,000 doses of Cervarix have been administered up to the end of February 2009. As of 20th May, MHRA had received 1710 Yellow Cards, including 3774 adverse-reaction terms. Majority of suspected adverse reactions related to signs and symptoms of either recognised/known adverse reactions that are listed in the product information or 'psychogenic events'. The most recent Safety Adverse Reaction Analysis reports can be found in the Annex.

With every major vaccine programme where many individuals are immunised in a short period of time, it is inevitable that some serious medical conditions will occur shortly after immunisation and be linked with the vaccine regardless of causality. Therefore, reports may be true side-effects or they may have been caused by coincidental medical conditions resulting from underlying or undiagnosed illness and, as such, would have occurred even in the absence of vaccination.

The MHRA has in place a proactive pharmacovigilance strategy to monitor the safety of Cervarix vaccine as it is used in the UK. Part of this includes comparing background age and sex-specific incidence rates (before the vaccine was introduced) of a wide range

of medical conditions (those which may naturally occur in adolescent females and be temporally associated with vaccination) with rates reported via the Yellow Card Scheme. These analyses adjust for various levels of possible under-reporting through the Scheme.

The following medical conditions were included in the observed-expected analysis:

2.2.1 Cervarix Vaccine and Facial Palsy

Facial Palsy naturally occurs in the population and it is therefore inevitable that cases will be reported as ADRs in temporal association with vaccination. MHRA has received one UK report of suspected facial palsy in association with vaccination with Cervarix vaccine. The observed-expected analysis indicates that facial palsy has not occurred after vaccination to a greater extent than would be expected based on background data before the vaccine was introduced. MHRA will keep this issue under close review.

2.2.2 Human Papillomavirus (HPV) vaccine and Guillain-Barre Syndrome (GBS)

Guillain-Barre Syndrome (GBS) is a rare neurological disorder that causes muscle weakness. Similarily to facial palsy, it naturally occurs in the population and is usually thought to be caused by a preceding infectious illness. An alleged association between Gardasil vaccine and GBS was discussed within Europe and the US in 2007. The U.S. Centres for Disease Control and Prevention (CDC) carefully reviewed reports of GBS after Gardasil vaccination that were submitted to the Vaccine Adverse Event Reporting System (VAERS). They found that 'there is no evidence that Gardasil has increased the rate of GBS above that expected in the population' and 'the data do not currently suggest an association between Gardasil and GBS'[1].

MHRA has received one UK report of suspected Guillain-Barre Syndrome in association with vaccination with Cervarix vaccine. In the UK, several hundred thousand doses of Cervarix have been given to girls through the national programme and there is no evidence that the vaccine has increased the frequency of GBS above that expected to occur naturally in the population. MHRA will keep this issue under close review.

2.2.3 Cervarix Vaccine and Chronic Fatigue Syndrome (CFS)

MHRA has received one UK report of Chronic fatigue syndrome (CFS) and three UK reports of post viral fatigue syndrome. Chronic fatigue syndrome (CFS) is not an uncommon condition amongst adolescents and rates are greater in females than in males. Given that almost 1 million doses of Cervarix have now been given in the UK, it

[1]U.S. Centers for Disease Control and Prevention – Information from FDA and CDC on Gardasil and its Safety: http://www.cdc.gov/vaccinesafety/vaers/FDA_and_CDC_Statement.htm

is inevitable that conditions such as CFS will occur not long after vaccination regardless of any causal association with the vaccine.

Because of alleged, though so far unproven, links between other vaccines given in adolescence (such as HepB vaccines) and CFS, the MHRA included CFS in the observed-expected analysis at the start of the immunisation programme.

This analysis shows that amongst the number of 12-13 yr old girls immunised so far in the UK, we would have expected to observe more than 60 new cases of CFS already regardless of vaccination. Therefore, the possible cases of CFS reported to us so far in temporal association with vaccination do not suggest that the vaccine carries any excess risk of CFS above the expected background rate. MHRA will keep this issue under close review.

Safeguarding public health

Suspected Adverse Reaction Analysis

CERVARIX Human papillomavirus (HPV) vaccine

21 May 2009

This report summarises the adverse reactions suspected to have been caused by Cervarix human papillomavirus (HPV) vaccine in the UK. This includes reports received between 14 April 2008 and 20 May 2009. These reports have been voluntarily submitted to the MHRA by healthcare professionals and members of the public via the Yellow Card Scheme (visit www.yellowcard.gov.uk) and by the manufacturers of the vaccine as part of their legal requirements.

It is essential to bear in mind that reports to the MHRA relate only to adverse medical events which the reporter considered could have been caused by the vaccine (i.e. if there was merely a **suspicion** of causality). Therefore, cases may be true side-effects or they may have been purely coincidental events due to underlying or undiagnosed illness that would have occurred anyway in the absence of vaccination. Events may also have been psychogenic[1] in origin. This report therefore cannot be considered to represent a list of known side-effects of the vaccine. These data also cannot be used to determine the frequency, or incidence, of known side-effects because they are often under-reported. The known side-effects, and their frequencies (based on clinical trial data), are available in the product information (see http://emc.medicines.org.uk/).

The reactions in this report have been broken down into 5 categories based on scientific assessment of individual cases by MHRA assessors: injection-site reactions; allergic reactions; 'psychogenic' events; other recognised reactions; and 'suspected adverse reactions not currently recognised' (reactions in this latter category are divided into the high-level classification of System Organ Class)[2]. The same event term may appear in more than one category (e.g. 'rash' may be associated with injection site, allergic or unrecognised suspected reactions and 'psychogenic' events). However, an event from a single report will appear in only one category.

A single report may contain more than one reaction, more than one sign or symptom of a single reaction or different reactions in more than one of the above categories. Therefore the total number of listed reactions is greater than the total number of reports and total reports in each of the 5 tables should not be added together.

Headline summary:

To date, the vast majority of suspected adverse reactions reported to MHRA in association with Cervarix vaccine have related either to the signs and symptoms of recognised side effects listed in the product information or were due to the injection process and not the vaccine itself (i.e. 'psychogenic' in nature).

For the isolated cases of other medical conditions reported, the available evidence does not suggest that the vaccine caused the condition and these may have been coincidental events.

The balance of risks and benefits of Cervarix remains positive.

[1] For this analysis, defined as non-allergic events which occurred within minutes of, or soon after, vaccination and were most likely a psychogenic response to, or anticipation of, the injection. These are not side effects to the vaccine as such and can occur with any needle injection procedure.
[2] Using MedDRA terminology

Medicines and Healthcare products Regulatory Agency
Market Towers 1 Nine Elms Lane London SW8 5NQ
T 020 7084 2000 F 020 7084 2353 www.mhra.gov.uk

SUMMARY OF UK SAFETY EXPERIENCE

Total number of reports received: 1,710
Total number of suspected reactions: 3,774
Estimated number of doses administered: at least 800,000 doses[3]

A. Injection-site reactions

Injection-site reactions including redness, pain and swelling are recognised side-effects of Cervarix vaccine and are listed in the product information. These may occur at a frequency[4] of more than 1 in 10 persons vaccinated. The reported cases of 'Pain in extremity' mainly relate to a sore arm.

The cases reported to the MHRA during use of the vaccine in the UK do not indicate any change in the severity or nature of injection-site reactions.

Reported event (Preferred Term[2])	Number of cases
Pain in extremity	170
Limb discomfort	50
Injection site swelling	45
Injection site pain	39
Injection site erythema	36
Hypoaesthesia	32
Oedema peripheral	27
Erythema	16
Injection site rash	16
Local reaction	11
Skin discolouration	11
Injection site mass	10
Pain	10
Injection site reaction	9
Musculoskeletal stiffness	9
Injection site pruritus	6
Injection site warmth	6
Injection site inflammation	5
Local swelling	5
Paraesthesia	5
Peripheral coldness	5
Rash macular	5
Contusion	4
Sensation of heaviness	4
Sensory disturbance	4
Injection site anaesthesia	3
Injection site discharge	3
Injection site induration	3
Muscular weakness	3
Myalgia	3
Asthenia	2
Feeling cold	2
Feeling hot	2
Inflammation	2

[3] Based on UK-wide vaccine uptake data to February 2009. As the Yellow Card data are up to the present date, the available uptake data should not be used to derive adverse reaction reporting rates (as this will result in an over-estimation)
[4] Based on clinical trial data

Injection site haematoma	2
Injection site infection	2
Injection site urticaria	2
Injection site vesicles	2
Limb immobilisation	2
Pruritus	2
Sensory loss	2
Cyanosis	1
Grip strength decreased	1
Immobile	1
Injection site discolouration	1
Injection site irritation	1
Injection site joint pain	1
Injection site papule	1
Injection site paraesthesia	1
Pallor	1
Rash pruritic	1
Scab	1
Sensation of pressure	1
Swelling	1
Urticaria	1
Total reactions	591
Total reports	430

B. Allergic reactions (including skin reactions not directly related to an injection-site reaction)

Allergic reactions are recognised side-effect of Cervarix vaccine and are listed in the product information. These may occur at a frequency[4] between 1 in 10 persons (for non-serious types of allergic reaction such as rash and itching) to less than 1 in 10,000 persons vaccinated. Severe allergic reactions are very rare.

The cases reported to the MHRA during use of the vaccine in the UK do not indicate any change in the severity or nature of allergic reactions.

Reported event (Preferred Term[2])	Number of cases
Rash	58
Urticaria	32
Pruritus	26
Oedema peripheral	18
Rash pruritic	18
Erythema	15
Swelling face	15
Rash generalised	12
Rash macular	12
Dyspnoea	11
Lip swelling	10
Eye swelling	9
Hypersensitivity	9
Paraesthesia oral	9
Anaphylactic reaction	7
Pruritus generalised	5

Throat tightness	5
Dizziness	4
Pallor	4
Paraesthesia	4
Pharyngeal oedema	4
Rash erythematous	4
Flushing	3
Dysphagia	2
Eye pruritus	2
Heart rate increased	2
Hyperventilation	2
Ocular hyperaemia	2
Peripheral coldness	2
Purpura	2
Rash maculo-papular	2
Throat irritation	2
Angioedema	1
Blister	1
Chest discomfort	1
Dermatitis	1
Dermatitis allergic	1
Eczema	1
Eyelid oedema	1
Feeling abnormal	1
Feeling hot	1
Generalised erythema	1
Gingival swelling	1
Hyperhidrosis	1
Hypertension	1
Hypoaesthesia	1
Limb discomfort	1
Malaise	1
Musculoskeletal stiffness	1
Nasopharyngitis	1
Nausea	1
Neck pain	1
Pain in extremity	1
Periorbital oedema	1
Petechiae	1
Respiratory rate increased	1
Skin irritation	1
Skin reaction	1
Sneezing	1
Speech disorder	1
Swelling	1
Swollen tongue	1
Syncope	1
Tachycardia	1
Type I hypersensitivity	1
Vomiting	1
Wheezing	1
Total reactions	347
Total reports	210

C. 'Psychogenic' events

Psychogenic events including vasovagal syncope, faints and panic attacks can occur with any injection procedure, not just vaccination, and can be common in adolescents. These are due to fear and/or anticipation of the needle injection and are **not side-effects of Cervarix vaccine** as such. Such events can be associated with a wide range of temporary signs and symptoms including loss of consciousness, vision disturbance, injury, limb jerking (often misinterpreted as a seizure/convulsion), limb numbness or tingling, difficulty in breathing, hyperventilation etc.

The events in the list below were considered 'psychogenic' in nature based on MHRA assessment of the individual case details reported. The reported cases which do not refer specifically to vasovagal syncope, faint or panic attack (e.g. convulsion, transient blindness which refers to temporary loss of vision at the start of a faint) were concurrently reported as signs or symptom of the psychogenic event; **i.e. these also were not side-effects of the vaccine itself**.

Reported event (Preferred Term[2])	Number of cases
Syncope	145
Dizziness	144
Nausea	72
Headache	62
Pallor	53
Malaise	39
Tremor	32
Vomiting	30
Flushing	26
Feeling hot	22
Cold sweat	20
Vision blurred	19
Paraesthesia	12
Presyncope	12
Hyperhidrosis	10
Loss of consciousness	9
Rash	9
Chills	7
Heart rate increased	7
Muscle twitching	7
Somnolence	7
Tearfulness	7
Unresponsive to stimuli	7
Dyskinesia	6
Dyspnoea	6
Hypoaesthesia	6
Muscle rigidity	6
Pyrexia	6
Visual impairment	6
Abdominal pain upper	5
Asthenia	5
Convulsion	5
Erythema	5
Eye rolling	5
Fatigue	5
Feeling cold	5

Feeling of body temperature change	5
Hyperventilation	5
Nervousness	5
Panic attack	5
Tachycardia	5
Abdominal pain	4
Blindness transient	4
Chest discomfort	4
Feeling abnormal	4
Muscular weakness	4
Peripheral coldness	4
Rash macular	4
Body temperature increased	3
Confusional state	3
Dysgeusia	3
Fall	3
Mydriasis	3
Nasopharyngitis	3
Pain	3
Pulse abnormal	3
Throat tightness	3
Abasia	2
Abdominal discomfort	2
Amnesia	2
Anxiety	2
Disorientation	2
Disturbance in attention	2
Dizziness postural	2
Heart rate irregular	2
Hot flush	2
Hypertension	2
Lethargy	2
Muscle spasms	2
Myalgia	2
Neck pain	2
Photophobia	2
Pruritus	2
Retching	2
Skin discolouration	2
Tinnitus	2
Urticaria	2
Agitation	1
Altered state of consciousness	1
Anorexia	1
Blood pressure decreased	1
Bruxism	1
Burning sensation	1
Chest pain	1
Cough	1
Cyanosis	1
Deafness	1
Deafness transitory	1
Depressed level of consciousness	1
Discomfort	1

Dry mouth	1
Dry throat	1
Dysarthria	1
Dysphagia	1
Dysstasia	1
Ear pain	1
Eyelid oedema	1
Face injury	1
Facial spasm	1
Feeling drunk	1
Feeling of despair	1
Grand mal convulsion	1
Head discomfort	1
Hypersomnia	1
Hypokinesia	1
Hypotension	1
Lip swelling	1
Livedo reticularis	1
Musculoskeletal stiffness	1
Nervous system disorder	1
Oropharyngeal pain	1
Pain in extremity	1
Palpitations	1
Panic reaction	1
Rash generalised	1
Respiratory arrest	1
Respiratory rate decreased	1
Respiratory rate increased	1
Salivary hypersecretion	1
Seizure anoxic	1
Sensation of heaviness	1
Sensory loss	1
Shock	1
Sinus tachycardia	1
Sleep attacks	1
Throat irritation	1
Vertigo	1
Total reactions	999
Total reports	382

D. 'Other recognised' reactions

This section includes other events recognised to be side-effects of Cervarix vaccine and not already included in sections A and B above. This also includes signs and symptoms of recognised side effects. The frequencies, where known, are listed in the product information.

The cases reported to the MHRA during use of the vaccine in the UK so far do not indicate any change in the severity or nature of these reactions.

Reported event (Preferred Term[2])	Number of cases
Nausea	270
Headache	265
Dizziness	239
Vomiting	104
Malaise	86
Fatigue	71
Pyrexia	67
Abdominal pain	36
Abdominal pain upper	27
Myalgia	26
Feeling hot	20
Diarrhoea	19
Arthralgia	16
Body temperature increased	14
Lethargy	14
Pain	12
Chills	9
Oropharyngeal pain	9
Paraesthesia	9
Abdominal discomfort	8
Pallor	8
Somnolence	7
Asthenia	5
Musculoskeletal stiffness	5
Pain in extremity	5
Pruritus	5
Influenza like illness	4
Back pain	3
Flushing	3
Hypoaesthesia	3
Neck pain	3
Anorexia	2
Cough	2
Head discomfort	2
Joint swelling	2
Listless	2
Photophobia	2
Rash	2
Skin warm	2
Syncope	2
Abdominal pain lower	1
Body temperature fluctuation	1
Erythema	1
Feeling cold	1

Feeling of body temperature change	1
Hot flush	1
Hyperhidrosis	1
Ill-defined disorder	1
Induration	1
Local swelling	1
Lower respiratory tract infection	1
Migraine	1
Muscle twitching	1
Muscular weakness	1
Musculoskeletal chest pain	1
Musculoskeletal pain	1
Nasal congestion	1
Nervousness	1
Peripheral coldness	1
Pharyngitis	1
Pruritus generalised	1
Psoriasis	1
Respiratory disorder	1
Restlessness	1
Thirst	1
Tremor	1
Upper respiratory tract infection	1
Urticaria	1
Total reactions	1418
Total reports	765

E. Suspected adverse reactions not currently recognised

This section includes reports which, based on MHRA assessment of the case details provided, do not fit into one of the above 4 categories.

These suspected ADRs are not currently recognised as side effects of Cervarix vaccine and the available evidence does not suggest a causal link with the vaccine. These are isolated medical events which may have been coincidental with vaccination. These reports are continually assessed by the MHRA.

Guillain Barre Syndrome (GBS) naturally occurs in the population and is usually thought to be caused by a preceding infectious illness. Several hundred thousand doses of Cervarix have been given to girls and there is no evidence that the vaccine has increased the frequency of GBS above that expected to occur naturally in the population.

System Organ Class	Reported event (Preferred Term[2])	Number of cases
Blood and lymphatic system disorders	Lymphadenopathy	9
Cardiac disorders	Cyanosis	1
	Palpitations	3
	Sinus tachycardia	1
Ear and labyrinth disorders	Ear pain	6
	Tinnitus	1

Eye disorders	Dry eye	1
	Excessive eye blinking	1
	Eye swelling	1
	Photophobia	1
	Vision blurred	5
	Visual impairment	2
Gastrointestinal disorders	Abdominal pain lower	1
	Abdominal pain upper	1
	Abnormal faeces	1
	Colitis ulcerative	1
	Diarrhoea	3
	Flatulence	1
	Mouth ulceration	1
	Nausea	6
	Vomiting	5
General disorders and administration site conditions	Abasia	3
	Axillary pain	1
	Chest discomfort	3
	Chest pain	7
	Chills	3
	Chronic fatigue syndrome	1
	Fatigue	6
	Feeling abnormal	1
	Feeling cold	3
	Feeling hot	1
	Gait disturbance	2
	Influenza like illness	15
	Injection site reaction	1
	Local swelling	1
	Malaise	5
	Oedema peripheral	3
	Pain	5
	Pyrexia	3
	Sensation of foreign body	1
	Swelling	1
	Thirst	1
Infections and infestations	Acarodermatitis	1
	Application site pustules	1
	Folliculitis	1
	Impetigo	1
	Influenza	1
	Lower respiratory tract infection	1
	Nasopharyngitis	3
	Pneumonia viral	1
	Post viral fatigue syndrome	3
	Streptococcal sepsis	1
	Urinary tract infection	2
	Viral infection	3
Injury, poisoning and procedural complications	Contusion	3
	Drug exposure during pregnancy	2

Investigations	Blood glucose increased	3
	Blood pressure abnormal	1
	Blood pressure increased	1
	Body temperature increased	1
	Respiratory rate increased	1
	Weight decreased	2
Metabolism and nutrition disorders	Anorexia	2
	Decreased appetite	2
	Dehydration	1
	Diabetes mellitus inadequate control	1
	Diabetic ketoacidosis	1
	Hypoglycaemia	1
	Increased appetite	1
	Type 1 diabetes mellitus	2
Musculoskeletal and connective tissue disorders	Arthralgia	3
	Back pain	3
	Bone pain	1
	Flank pain	1
	Muscle spasms	2
	Muscle twitching	2
	Muscular weakness	9
	Musculoskeletal chest pain	1
	Musculoskeletal stiffness	4
	Myalgia	2
	Neck pain	3
	Pain in extremity	15
	Palindromic rheumatism	1
	Sensation of heaviness	1
Nervous system disorders	Ataxia	1
	Complex regional pain syndrome	1
	Convulsion	7
	Coordination abnormal	1
	Crying	2
	Dizziness	7
	Dysarthria	1
	Dysstasia	2
	Epilepsy	2
	Facial palsy	1
	Grand mal convulsion	1
	Guillain-barre syndrome	1
	Headache	10
	Hemiparesis	1
	Hypoaesthesia	5
	Lethargy	2
	Loss of consciousness	3
	Migraine	9
	Migraine with aura	1
	Myoclonic epilepsy	1

	Optic neuritis	1
	Paraesthesia	4
	Partial seizures	1
	Psychomotor hyperactivity	1
	Sensory disturbance	3
	Sensory loss	2
	Somnolence	10
	Status epilepticus	1
	Syncope	10
	Tremor	3
	Unresponsive to stimuli	1
	Visual field defect	3
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	3
Psychiatric disorders	Abnormal behaviour	1
	Aggression	1
	Anxiety	1
	Confusional state	1
	Dysphemia	1
	Eating disorder	1
	Emotional disorder	1
	Fear	1
	Hallucination, visual	1
	Insomnia	3
	Screaming	1
	Sleep disorder	2
	Somatisation disorder	1
Renal and urinary disorders	Urinary incontinence	1
Reproductive system and breast disorders	Amenorrhoea	1
	Breast pain	1
	Breast swelling	1
	Breast tenderness	1
	Menorrhagia	1
	Menstrual disorder	1
	Menstruation irregular	1
	Metrorrhagia	1
	Vaginal discharge	1
	Vaginal haemorrhage	3
	Vulval ulceration	1
Respiratory, thoracic and mediastinal disorders	Asthma	3
	Cough	2
	Dyspnoea	10
	Epistaxis	3
	Haemoptysis	1
	Hypoventilation	1
	Nasal congestion	1
	Oropharyngeal blistering	1
	Oropharyngeal pain	5
	Rhinorrhoea	1
	Wheezing	2
Skin and subcutaneous	Acne	1

tissue disorders	Alopecia	4
	Alopecia areata	1
	Blister	2
	Eczema	4
	Erythema	2
	Erythema multiforme	1
	Guttate psoriasis	1
	Hyperhidrosis	1
	Hypoaesthesia facial	1
	Rash	3
	Rash maculo-papular	1
	Rash vesicular	1
	Skin discolouration	4
	Skin exfoliation	1
	Skin hypertrophy	1
	Skin lesion	1
	Stevens-Johnson syndrome	1
	Trichorrhexis	1
	Urticaria	2
Vascular disorders	Circulatory collapse	1
	Flushing	1
	Haemorrhage	1
	Hot flush	1
	Hypotension	1
	Pallor	1
	Peripheral coldness	6
Total reactions		419
Total reports		243

In relation to safety in pregnancy, during pre-licensing studies of Cervarix it was found that almost 870 women became pregnant before or after receiving the vaccine. The overall rates of spontaneous abortion in these clinical trials were no greater than the background rates in the general population (i.e. regardless of vaccination). There is currently no evidence to suggest that Cervarix vaccine carries any risks during pregnancy. Nonetheless, Cervarix is not recommended for use in pregnancy.

Safeguarding public health

Suspected Adverse Reaction Analysis

Human papillomavirus (HPV) vaccine (brand unspecified)

21 May 2009

This report summarises the reports of adverse reactions suspected to have been caused by human papillomavirus (HPV) vaccine for which information on the specific brand administered (whether Cervarix or Gardasil) is currently unavailable. This includes reports received up to 20 May 2009. Separate Adverse Reaction Analysis summaries exist for reports in which the brand was stated. These reports have been voluntarily submitted to the MHRA by healthcare professionals and members of the public via the Yellow Card Scheme (visit www.yellowcard.gov.uk) and by the manufacturers of the vaccine as part of their legal requirements.

It is essential to bear in mind that reports to the MHRA relate only to adverse medical events which the reporter considered could have been caused by the vaccine (i.e. if there was merely a **suspicion** of causality). Therefore, cases may be true side-effects or they may have been purely coincidental events due to underlying or undiagnosed illness that would have occurred anyway in the absence of vaccination. Events may also have been psychogenic[1] in origin. This report therefore cannot be considered to represent a list of known side-effects of the vaccine. These data also cannot be used to determine the frequency, or incidence, of known side-effects because they are often under-reported. The known side-effects, and their frequencies (based on clinical trial data), are available in the product information (see http://emc.medicines.org.uk/).

The reactions in this report have been broken down into 5 categories based on scientific assessment of individual cases by MHRA assessors: injection-site reactions; allergic reactions; 'psychogenic' events; other recognised reactions; and 'suspected adverse reactions not currently recognised' (reactions in this latter category are divided into the high-level classification of System Organ Class)[2]. The same event term may appear in more than one category (e.g. 'rash' may be associated with injection site, allergic or unrecognised suspected reactions and 'psychogenic' events). However, an event from a single report will appear in only one category.

A single report may contain more than one reaction, more than one sign or symptom of a single reaction or different reactions in more than one of the above categories. Therefore the total number of listed reactions is greater than the total number of reports and total reports in each of the 5 tables should not be added together.

Headline summary:

To date, most suspected ADRs reported to MHRA in association with HPV vaccine have related to the signs and symptoms of recognised side effects listed in the product information or were due to the injection process and not the vaccine itself (i.e. 'psychogenic' in nature).

For the isolated case of other medical conditions reported, the available evidence does not suggest that the vaccine caused the condition and these may have been coincidental events.

The balance of risks and benefits of HPV vaccine remains positive.

[1] For this analysis, defined as non-allergic events which occurred within minutes of, or soon after, vaccination and were most likely a psychogenic response to, or anticipation of, the injection. These are not side effects to the vaccine as such and can occur with any needle injection procedure.
[2] Using MedDRA terminology

Medicines and Healthcare products Regulatory Agency
Market Towers 1 Nine Elms Lane London SW8 5NQ
T 020 7084 2000 F 020 7084 2353 www.mhra.gov.uk

An executive agency of the Department of Health

SUMMARY OF UK SAFETY EXPERIENCE

Total number of reports received: 97
Total number of suspected reactions: 275
Estimated number of doses of Cervarix administered: at least 800,000 doses[3]

A. Injection-site reactions

Injection-site reactions including redness, pain and swelling are recognised[4] side-effects of HPV vaccines and are listed in the product information. These may occur at a frequency[5] of more than 1 in 10 persons vaccinated.

The cases reported to the MHRA during use of the vaccine in the UK do not indicate any change in the severity or nature of injection site reactions.

Reported event (Preferred Term[2])	Number of cases
Erythema	4
Pain in extremity	4
Oedema peripheral	3
Injection site erythema	2
Pain	2
Pruritus	2
Skin reaction	2
Feeling hot	1
Injection site coldness	1
Injection site discolouration	1
Injection site haemorrhage	1
Injection site mass	1
Local swelling	1
Musculoskeletal stiffness	1
Rash	1
Urticaria	1
Total reactions	28
Total reports	16

[3] Based on UK-wide vaccine uptake data to February 2009. As the Yellow Card data are up to the present date, the available uptake data should not be used to derive adverse reaction reporting rates (as this will result in an over-estimation)
[4] Known to be associated with either Cervarix or Gardasil
[5] Based on clinical trial data

B. Allergic reactions (including skin reactions not directly related to an injection-site reaction)

Allergic reactions are a recognised[4] side-effect of HPV vaccines and are listed in the product information. These may occur at a frequency[5] between 1 in 10 persons (for non-serious types of allergic reaction such as rash and itching) to less than 1 in 10,000 persons vaccinated. Severe allergic reactions are very rare.

The cases reported to the MHRA during use of the vaccine in the UK do not indicate any change in the severity or nature of allergic reactions.

Reported event (Preferred Term[2])	Number of cases
Rash	5
Erythema	3
Eyelid oedema	3
Hypersensitivity	3
Urticaria	3
Pharyngeal oedema	2
Rash pruritic	2
Anaphylactic reaction	1
Blister	1
Dysphagia	1
Dyspnoea	1
Heat rash	1
Laryngeal oedema	1
Lip swelling	1
Pruritus	1
Rash erythematous	1
Rash generalised	1
Rash macular	1
Stridor	1
Swelling	1
Throat irritation	1
Throat tightness	1
Total reactions	36
Total reports	20

C. 'Psychogenic' events

Psychogenic events including vasovagal syncope, faints and panic attacks can occur with any injection procedure, not just vaccination, and can be common in adolescents. These are due to fear and/or anticipation of the needle injection and are not side-effects of HPV vaccine as such. Such events can be associated with a wide range of temporary signs and symptoms including loss of consciousness, vision disturbance, injury, limb jerking (often misinterpreted as a seizure/convulsion), limb numbness or tingling, difficulty in breathing, hyperventilation etc.

Reported event (Preferred Term[2])	Number of cases
Syncope	17
Headache	8
Dizziness	7
Pallor	4
Nausea	3
Dyspnoea	2
Presyncope	2
Rash	2
Vomiting	2
Abdominal pain	1
Asthenia	1
Back pain	1
Blindness transient	1
Blood pressure increased	1
Convulsion	1
Heart rate increased	1
Heart rate irregular	1
Hot flush	1
Hypoaesthesia	1
Malaise	1
Muscular weakness	1
Sensory loss	1
Somnolence	1
Urticaria	1
Vision blurred	1
Visual impairment	1
Total reactions	64
Total reports	27

D. 'Other recognised' reactions

This section includes other events recognised[4] to be side-effects of HPV vaccine and not already included in sections A and B above. This also includes signs and symptoms of recognised side effects. The frequencies, where known, are listed in the product information.

The cases reported to the MHRA during use of the vaccine in the UK so far do not indicate any change in the severity or nature of these reactions.

Reported event (Preferred Term[2])	Number of cases
Pyrexia	8
Headache	7
Nausea	6
Malaise	5
Vomiting	4
Dizziness	3
Fatigue	3
Abdominal pain	2
Somnolence	2
Abdominal pain upper	1
Body temperature increased	1
Diarrhoea	1
Hypoaesthesia	1
Lethargy	1
Lymphadenopathy	1
Musculoskeletal stiffness	1
Myalgia	1
Total reactions	48
Total reports	26

E. 'Suspected adverse reactions not currently recognised'

This section includes reports which, based on MHRA assessment of the case details provided, do not fit into one of the above 4 categories.

These suspected ADRs are not currently recognised as side effects of HPV vaccine and the available evidence does not suggest a causal link with the vaccine. These are isolated medical events which may have been coincidental with vaccination. These reports are continually assessed by the MHRA.

System Organ Class	Reported event (Preferred Term[2])	Number of cases
Ear and labyrinth disorders	Ear pain	1
	Hyperacusis	1
Eye disorders	Diplopia	1
	Photopsia	1
	Vision blurred	1
	Visual impairment	1
Gastrointestinal disorders	Abdominal discomfort	1
	Abdominal pain	2
	Abdominal pain upper	1
	Diarrhoea	1
	Nausea	3
General disorders and administration site conditions	Chills	1
	Discomfort	1
	Exercise tolerance decreased	1
	Fatigue	1
	Feeling abnormal	1
	Gait disturbance	1
	Influenza like illness	8
	Injection site swelling	1
	Local swelling	1
	Pain	2
	Pyrexia	2
	Temperature intolerance	1
	Thirst	1
Infections and infestations	Labyrinthitis	1
	Skin infection	1
Investigations	Body temperature increased	1
Musculoskeletal and connective tissue disorders	Arthralgia	1
	Back pain	1
	Joint stiffness	1
	Muscular weakness	1
	Musculoskeletal stiffness	1
	Pain in extremity	1
Nervous system disorders	Cerebellar ataxia	1
	Chorea	1
	Complex regional pain syndrome	1
	Dizziness	3

	Dizziness postural	1
	Dyskinesia	1
	Epilepsy	1
	Grand mal convulsion	1
	Headache	4
	Hypoaesthesia	3
	IVth nerve paralysis	1
	Lethargy	2
	Loss of consciousness	3
	Migraine	1
	Paraesthesia	2
	Petit mal epilepsy	1
	Tremor	1
Psychiatric disorders	Confusional state	2
	Depression	1
	Insomnia	1
Renal and urinary disorders	Neurogenic bladder	1
	Urinary retention	1
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1
	Nasal congestion	1
	Oropharyngeal pain	1
	Wheezing	1
Skin and subcutaneous tissue disorders	Acne	1
	Erythema multiforme	1
	Henoch-schonlein purpura	1
	Petechiae	1
	Photosensitivity reaction	1
	Purpura	2
	Rash	4
	Rash erythematous	1
	Skin discolouration	1
	Skin disorder	1
	Urticaria	1
Vascular disorders	Peripheral coldness	1
Total reactions		99
Total reports		30