Paper provided by MHRA for Joint Committee on Vaccination and Immunisation June 2008: VACCINE-ASSOCIATED SUSPECTED ADVERSE REACTIONS REPORTED VIA THE YELLOW CARD SCHEME DURING 2007

June 2008

CONTENTS

Introduction

This paper was prepared by Medicines and Healthcare products Regulatory Agency (MHRA) for the June 2008 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 to 31st December 2007.

Section 2 provides an update on key vaccine safety papers considered by CHM's Biologicals and Vaccines Expert Advisory Group (BVEAG) and/or its Pharmacovigilance Expert Advisory Group (PEAG) during 2007 and to date.

Prepared; May 2008

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 temporal association and the 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 either by regulatory criteria or by individual reporter judgement. Yellow Card data cover 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). Precise vaccine exposure data for 2007 were not available at the time of writing this report. 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 2007.

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

	Sep-Dec 2006	2007
Total Number of Reports	11 (6)	60 (28)
Total Number of Reactions	24 (5)	144 (18)
Total Fatal	0 0	
Exposure	200,000 58	5,000
ERR per 100,000 doses	5.5 (3)	10.3 (3.8)

ERR = Estimated Reporting Rate

The estimated reporting rates are based on imprecise data and assumptions and therefore no firm conclusions can be drawn on these. However, the slight increase in serious ADR reporting rate raises no specific concerns.

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

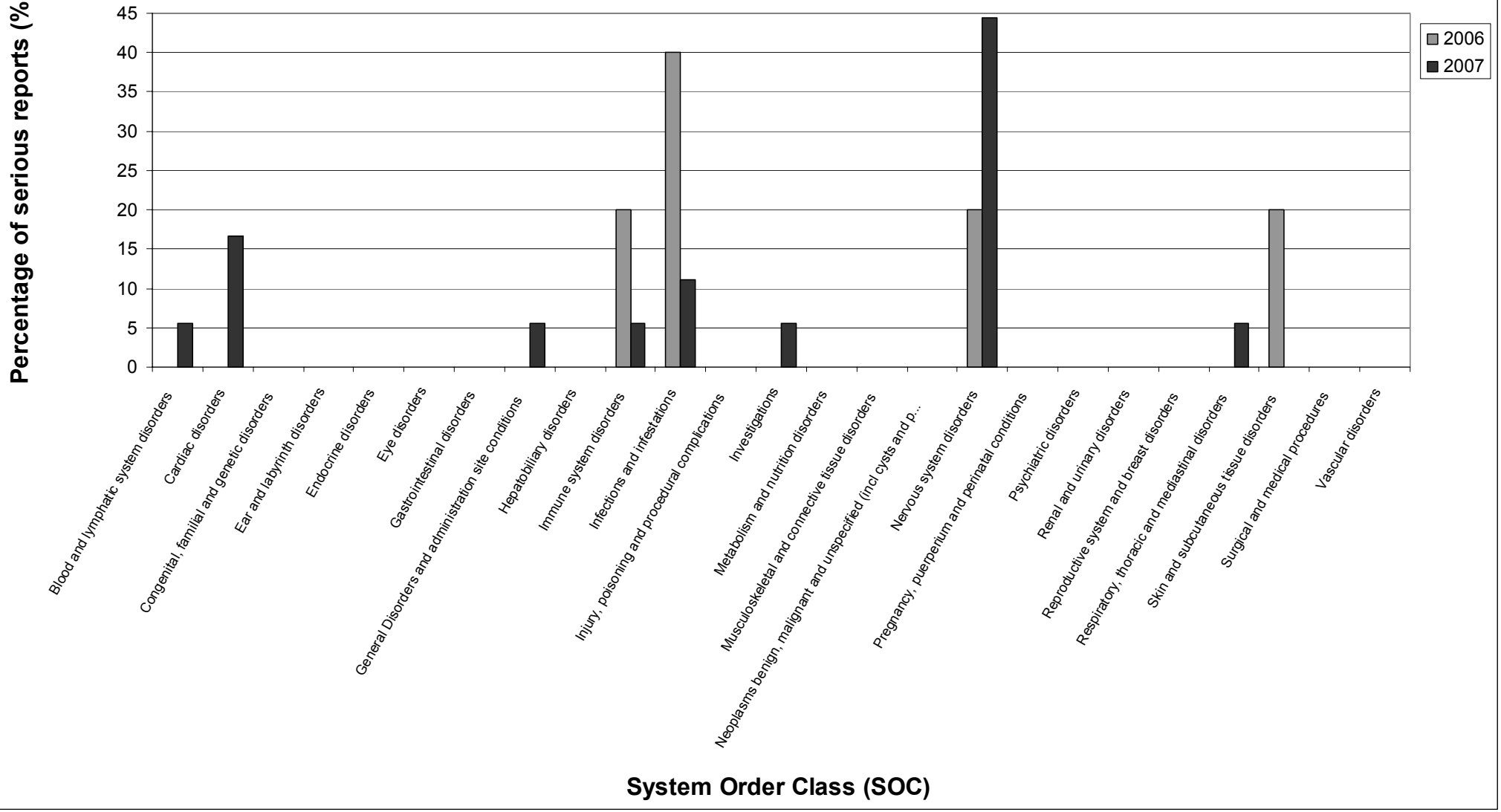
Table 2: Serious ADRs reported for Menitorix

Serious Suspected ADR		No of reports
Systen Organ Class (SOC)	**Preferred Term (PT)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	LYMPHADENOPATHY	1
CARDIAC DISORDERS	BRADYCARDIA	2
	TACHYCARDIA	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	CHEST DISCOMFORT	1
IMMUNE SYSTEM DISORDERS	ANAPHYLACTIC REACTION	1
INFECTIONS AND INFESTATIONS	BRONCHITIS	1
	OSTEOMYELITIS	1
INVESTIGATIONS	BODY TEMPERATURE FLUCTUATION	1
NERVOUS SYSTEM DISORDERS	EPILEPSY	1
	FEBRILE CONVULSION	3
	HYPOTONIA	2
	PSYCHOMOTOR HYPERACTIVITY	1
	SYNCOPE VASOVAGAL	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	WHEEZING	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. Majority of the serious ADRs reported for Menitorix vaccine in 2007 belonged to the 'Nervous system disorders' SOC, followed by the 'Cardiac disorders' SOC. There has been an increase in the number of ADRs reported in the 'Nervous system disorders' SOC, with a 2-fold increase in percentage of serious reactions. However, overall numbers remain very small.

Conclusion: No significant new safety issues were identified during 2007.

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).

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

	2005	2006	2007
Total Number of Reports	6 (4)	335 (111)	294 (118)
Total Number of Reactions	16 (5)	690 (61)	673 (107)
Total Fatal	0	0	2
Exposure	n/a	1,500,000	1,800,000
ERR per 100,000 doses	n/a	22 (7)	16.3 (5.2)

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

Precise vaccine exposure data for 2007 were not available at the time of writing this report. 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 2007.

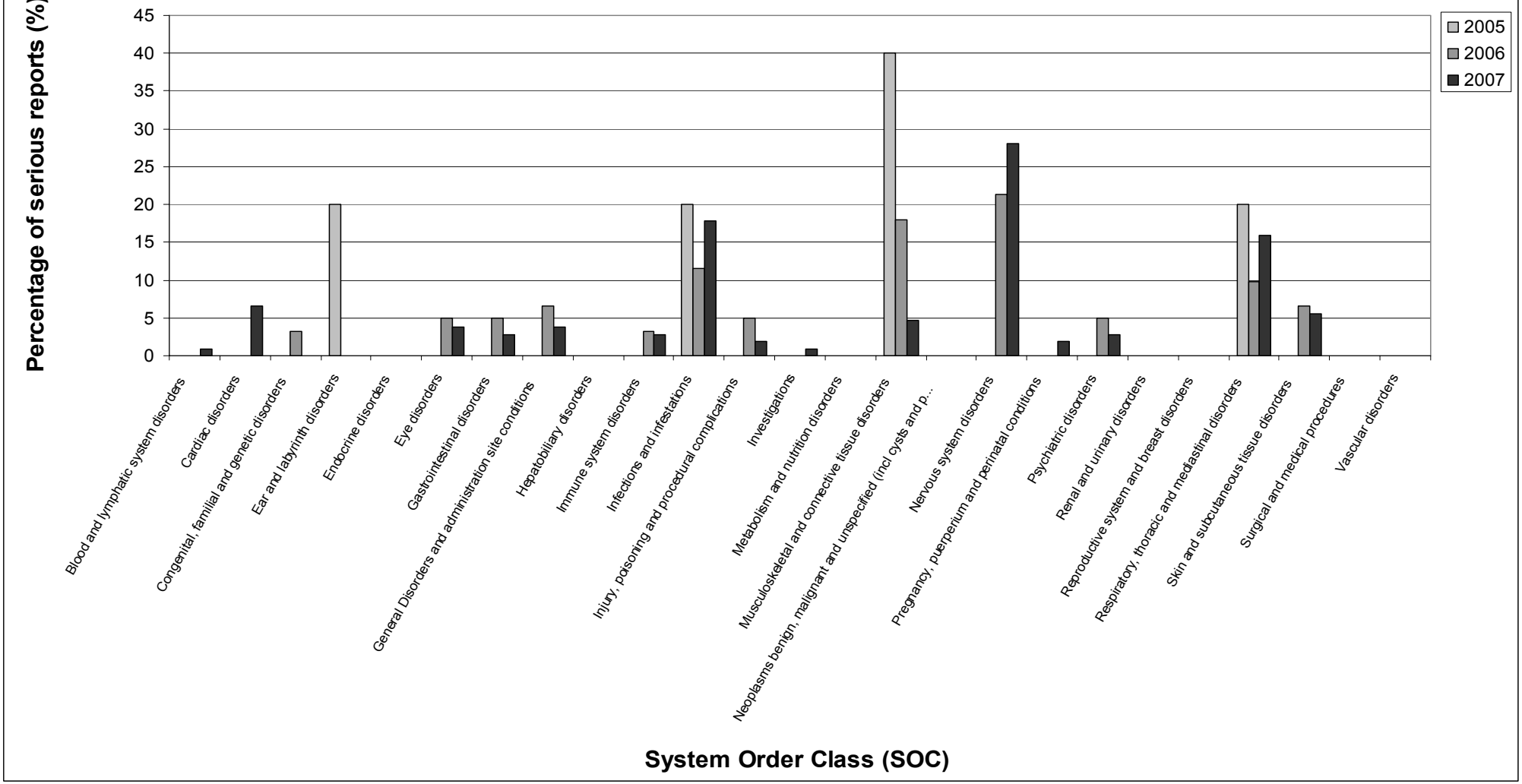
Figure 2 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. Majority of the serious ADRs reported for Prevenar vaccine in 2007 belonged to the 'Nervous system disorders' SOC, followed by the 'Infections and Infestation' SOC and the 'Respiratory, 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' (10 cases), followed by 'convulsion' (7 cases) and 'syncope' (4 cases).

One fatal report of death unexplained and one fatal report of sudden infant death syndrome was reported in 2007. A casual association with these fatal events has not been established.

Conclusion: No significant new safety issues were identified during 2007.

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). A Haemophilus influenzae type B (Hib) vaccine catch-up campaign was started in early September 2007. The use of Repevax (dTaP/IPV) and Infanrix IPV (DTaP/IPV) as pre-school boosters are being replaced with Infanrix IPV Hib (DTaP IPV Hib) vaccine (and possible Pediacel in a few cases). This campaign will be running until March 2009.

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

	2005	2006	2007
Total Number of Reports	198 (66)	115 (65)	171 (80)
Total Number of Reactions	370 (46)	251 (47)	405 (68)
Total Fatal	3	1	1
Exposure	1,833,000	1,833,000	2,000,000
ERR per 100,000 doses	10.7 (3.5)	4.9 (2.8)	8.5 (3.55)

ERR = Estimated Reporting Rate

The total number of ADRs increased in 2007 compared to 2006 but the number of reports was lower than 2005. This is partly explained by the increased exposure of the vaccine(s) as a pre-school booster. The distribution data for the vaccine during 2007 were not available at the time of writing this report and as such, ERRs have not been calculated. Taking account of the increased exposure as part of the Hib catch-up (pre-school boosters from Sep 2007), it is estimated that 2m doses of DTaP/IPV/Hib were administered during 2007 (assuming 90% uptake for an annual birth cohort of 650,000 (x3 doses), plus 1/3 of 650,000x0.9 [1dose]).

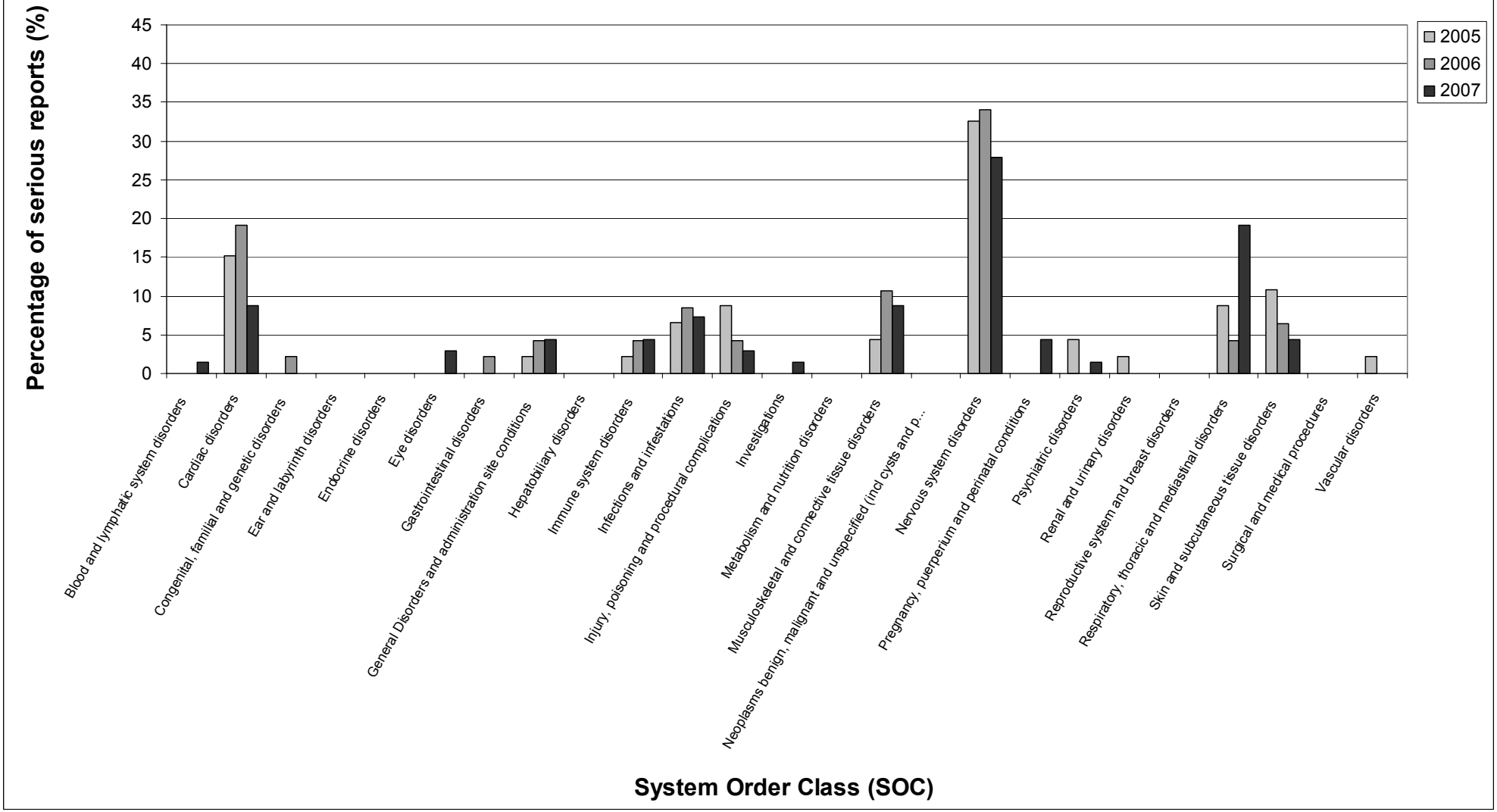
Based on this assumption of exposure, it is estimated that ADR reporting rates have increased. However, this conclusion must be treated with caution as more children may have been exposed as an early Hib catch-up. In addition, as Infanrix/IPV/Hib is a new product in the UK, it is expected that reporting would increase in the first few months of marketing. 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 2007 were broadly similar to those reported in the previous year. Approximately 28% 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 an increase in the number of serious ADRs in the 'Respiratory, thoracic and mediastinal disorders' SOC and a decrease in the 'Cardiac disorders' SOC.

One fatal report of sudden infant death syndrome was reported in 2007.

Conclusion: No significant new safety issues were identified during 2007.

Figure 3: Percentage of serious reactions per SOC associated with DTaP/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 doses of MMR were administered during 2007.

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

	2005	2006	2007
Total Number of Reports	203 (130)	151 (93)	100 (66)
Total Number of Reactions	419 (127)	338 (96)	295 (85)
Total Fatal	0	2	2
Exposure	1,105,000	1,105,000	1,105,000
ERR per 100,000 doses	18.4 (11.8)	11.8 (7.33)	9 (4.7)

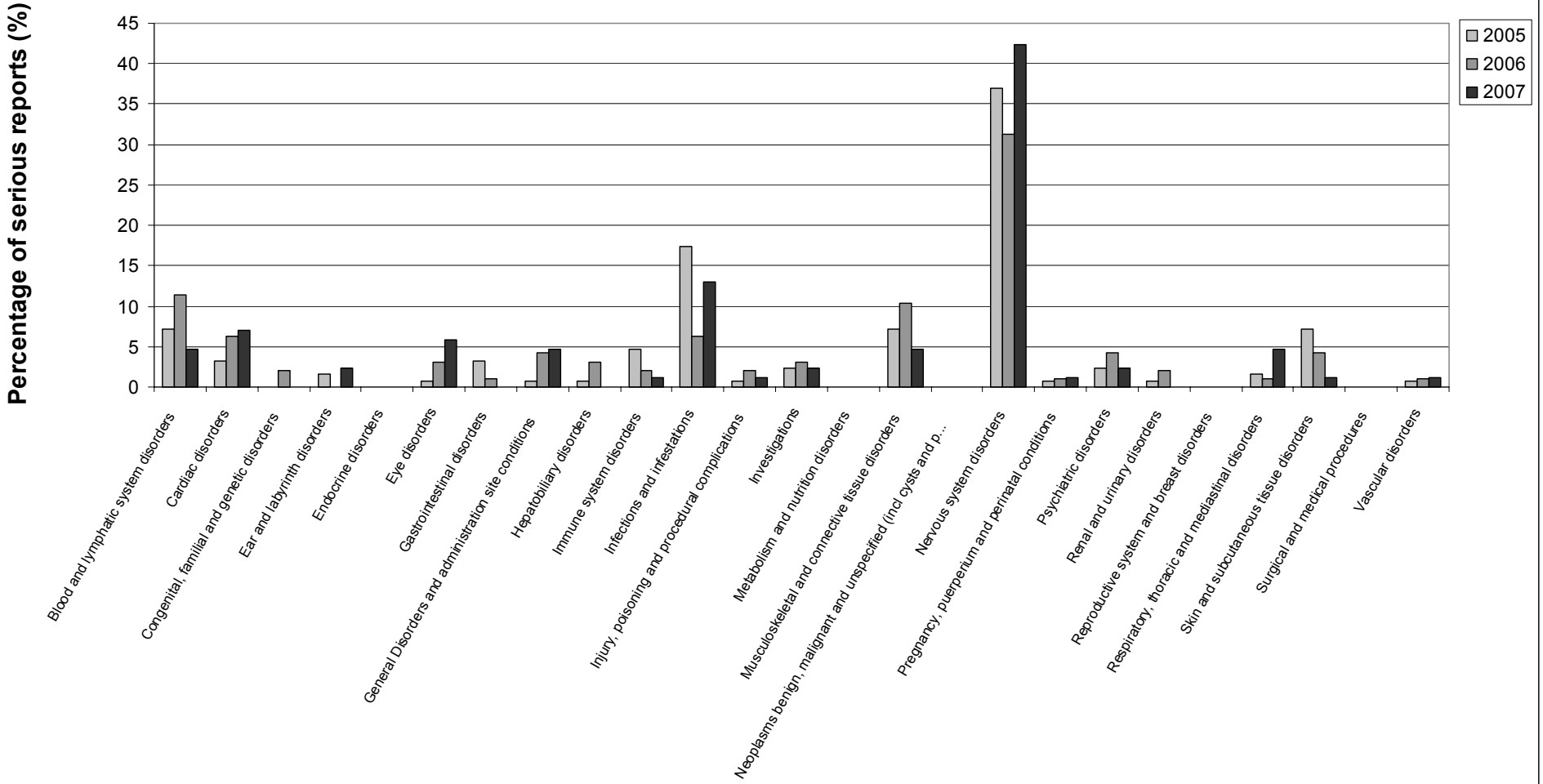
ERR = Estimated Reporting Rate

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' (16 cases) and 'encephalopathy' (5 cases).

There were 2 fatal reports of death unexplained reported during 2007. A casual association with these fatal events has not been established.

Conclusion: No significant new safety issues were identified during 2007.

Figure 4: Percentage of serious reactions per SOC associated with MMR vaccine



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)

	2005	2006	2007
Total Number of Reports	121 (59)	71 (43)	63 (29)
Total Number of Reactions	245 (47)	174 (36)	137 (28)
Total Fatal	2	1	0
Exposure	1,833,000	630,000	1,170,000
ERR per 100,000 doses	6.5 (3.2)	3.6 (2.1)	5.3 (2.1)

ERR = Estimated Reporting Rate

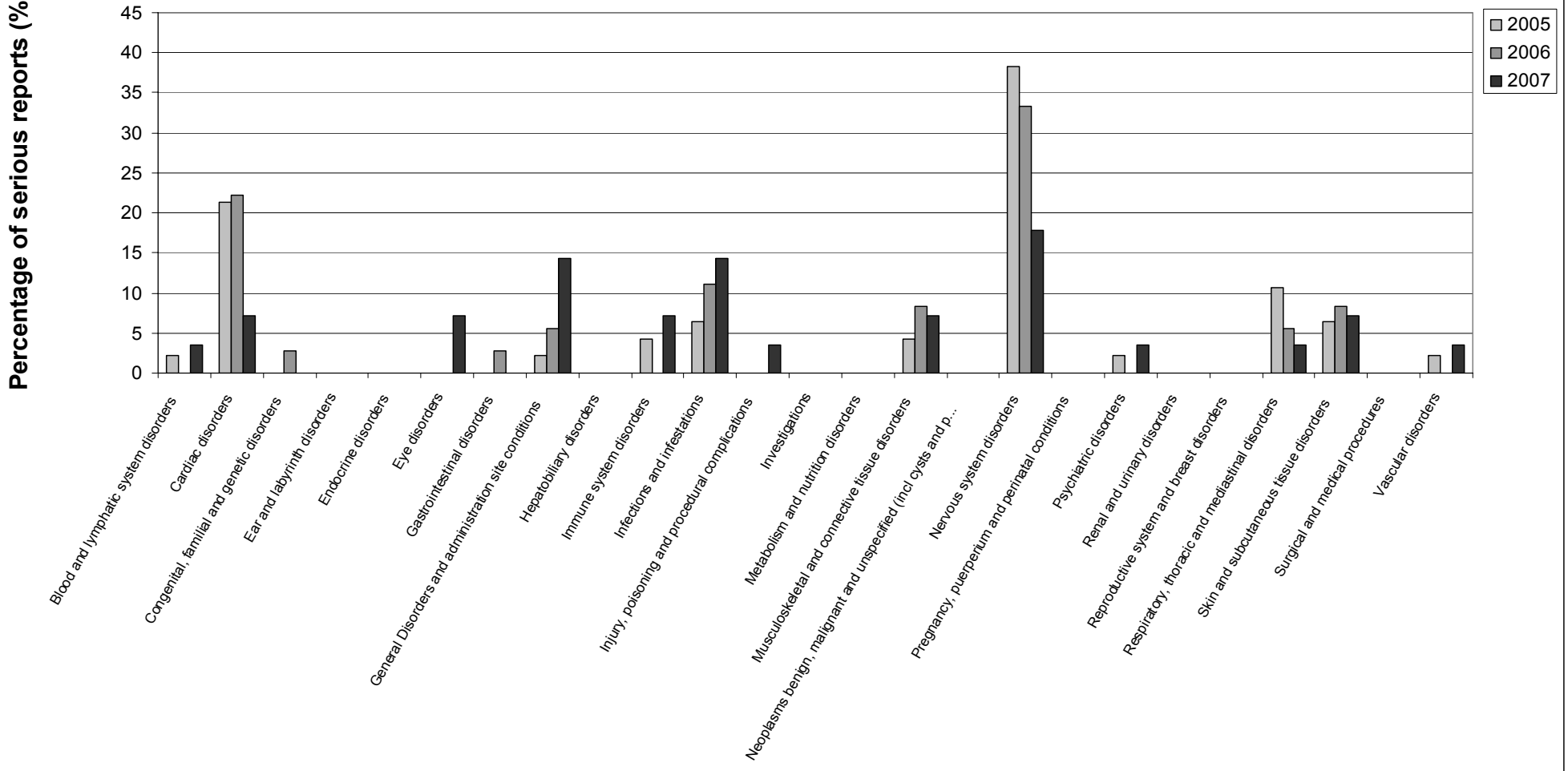
On the assumption of 90% uptake for an annual birth cohort of 650,000 (2 doses), it estimated that 1.17m doses of MenCC vaccines were administered during 2007.

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 'Unresponsive to stimuli' (2 cases). There were three cases of suspected vaccination failure, which occurred before the introduction of the MenC/Hib booster in Sep 2006.

No fatal reports were reported.

Conclusion: No significant new safety issues were identified during 2007.

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 2005.

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

	2005	2006	2007
Total Number of Reports	433 (126)	207 (81)	71 (30)
Total Number of Reactions	664 (53)	424 (49)	161 (15)
Total Fatal	0	0	0
Exposure	611,000	1,000	440,000
ERR per 100,000 doses	39 (11)	19 (9)	16 (5)

ERR = Estimated Reporting Rate

On the assumption of 90% uptake for an annual birth cohort of 650,000 (1 dose) x 0.75 (i.e. as the booster was routinely in place for only ¾ of 2007), it estimated that 440,000 doses of d/DTaP/IPV vaccines were administered during 2007.

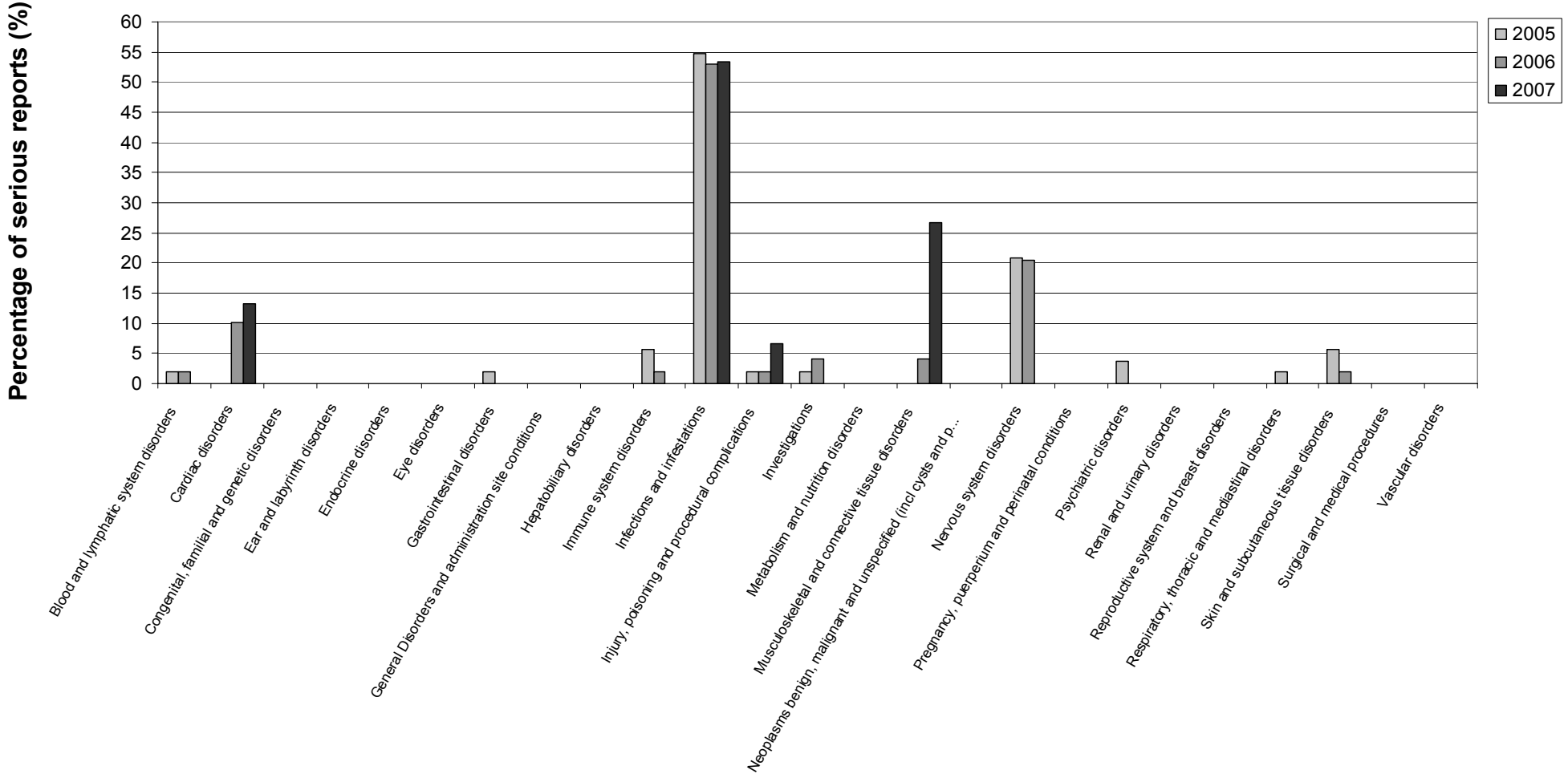
Figure 6 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. The majority of the serious reactions (53%) relate to the 'Infections and infestations' SOC, most common reaction for the past three years has been suspected cellulitis (most likely extensive injection site swelling mis-reported). A further quarter of total serious reactions (4 reactions) relate to the 'Musculoskeletal and connective tissue disorders' SOC.

Of all ADRs reported, most relate to injection site reactions and the most reported serious reactions are 'oedema peripheral' and 'erythema'. Extensive limb swelling is a recognised reaction to d/DTaP boosters, particularly when children have already received 3 or 4 doses of a DTaP-containing vaccine. However, there have been concerns in the UK over misdiagnosis of cellulitis, inappropriate hospitalisation and/or antibiotic treatment and unfounded suspicions over contaminated batches. Extensive limb swelling associated with these boosters has been reviewed by CHM's BVEAG in 2006.

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 2007.

Figure 6: Percentage of serious reactions per SOC associated with d/DTaP/IPV vaccine



1.1.7. Revaxis (dT/IPV)

Revaxis is a booster vaccine given to young people aged between 13 and 18. 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)

	2005	2006	2007
Total Number of Reports	177 (95)	80 (40)	109 (58)
Total Number of Reactions	492 (113)	214 (37)	323 (69)
Total Fatal	0	0	1
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.

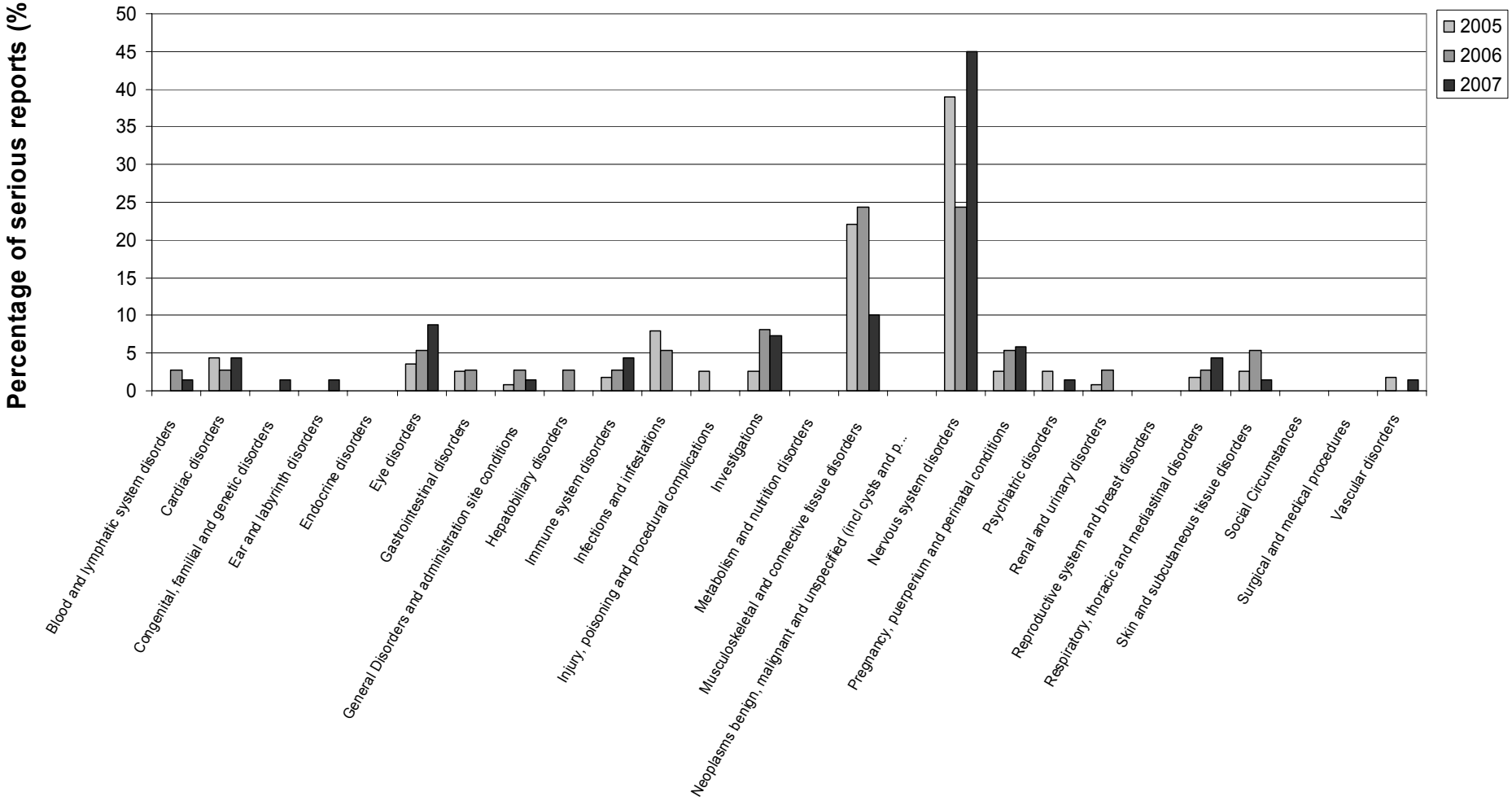
The total number of ADRs reported has increased by 29 reports for 2007 compared to 2006. The distribution data for the vaccine during 2007 were not available at the time of writing this report and as such, ERRs have not been calculated.

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 include nervous system disorders with 13 reports of syncope.

There was one fatal report of death unexplained associated with this vaccine in 2007. A casual association with the fatal event was not established.

Conclusion: No significant new safety issues have been identified during 2007.

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



1.2 New vaccines

1.2.1 Infanrix-IPV+Hib▼ (DTaP/IPV/Hib)

Infanrix-IPV+Hib was introduced to the routine childhood immunisation schedule in September 2007, in accordance with the Hib catch-up Campaign. The campaign was aimed at children who were too young to have received a Hib booster in a previous Hib campaign, and children who were too old to have received the MenC/Hib vaccine, Menitorix.

Please refer to Section 1.1.3. for the ADRs reported for the DTaP/IPV/Hib vaccines in 2007.

1.2.2 Gardasil▼ and Cervarix▼ (Human Papilloma Virus) vaccine

Gardasil was first authorised in September 2006 and Cervarix in November 2007, but they are not currently recommended for routine use. The HPV vaccine is being introduced to the routine immunisation schedule in September 2008. This will be offered to all girls aged 12-13 years to protect them against the risk of cervical cancer. There will also be an additional 2-year catch-up campaign starting in Autumn 2009, for girls aged up to 18 years. Three doses of the vaccine are required over a period of about six months.

The total number of suspected ADRs reported in association with Human Papilloma Virus (HPV) 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). The low number of suspected ADRs during 2007 reflects the fact that these vaccines have not yet been introduced into the routine immunisation schedule.

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

	2006	2007
Total Number of Reports	1 (1)	6 (4)
Total Number of Reactions	4 (1)	15 (6)
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.

The distribution data for the vaccine during 2007 were not available at the time of writing this report and as such, ERRs have not been calculated.

Table 10 lists the serious ADRs reported (note – one Yellow Card may contain more than one serious ADR). Seriousness is determined either by regulatory criteria or by reporter judgement.

Table 10: Serious ADRs reported for HPV

Serious Suspected ADR		No of reports
Systen Organ Class (SOC)	**Preferred Term (PT)**	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	MYALGIA	2
NERVOUS SYSTEM DISORDERS	CONVULSION	1
	SYNCOPE	1
PSYCHIATRIC DISORDERS	ACUTE PSYCHOSIS	1
VASCULAR DISORDERS	HYPOTENSION	1

[redacted]

An issue currently under discussion within Europe and the US is an alleged associated between Gardasil and Guillain Barre Syndrome (GBS). On the basis of around 35 cases in the post-marketing period (mostly in the US but also a few in Germany) following distribution of more than 23million doses worldwide, although a causal association with Gardasil has not been established, a consensus has been reached that the European product information should include GBS as a possible side effect. The manufacturer has been asked to assess this possible risk through a formal epidemiological study.

Conclusion: Other than GBS, no significant new safety issues have been identified during 2007

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 11).

Table 11: Total number of Hepatitis B vaccine reports and doses distributed (serious reports in brackets)

	2005	2006	2007
Total Number of Reports	126 (90)	115 (82)	130 (86)
Total Number of Reactions	482 (133)	410 (108)	352 (93)
Total Fatal	0	0	0
Exposure	n/a	n/a	n/a
ERR per 100,000 doses	n/a	n/a	n/a

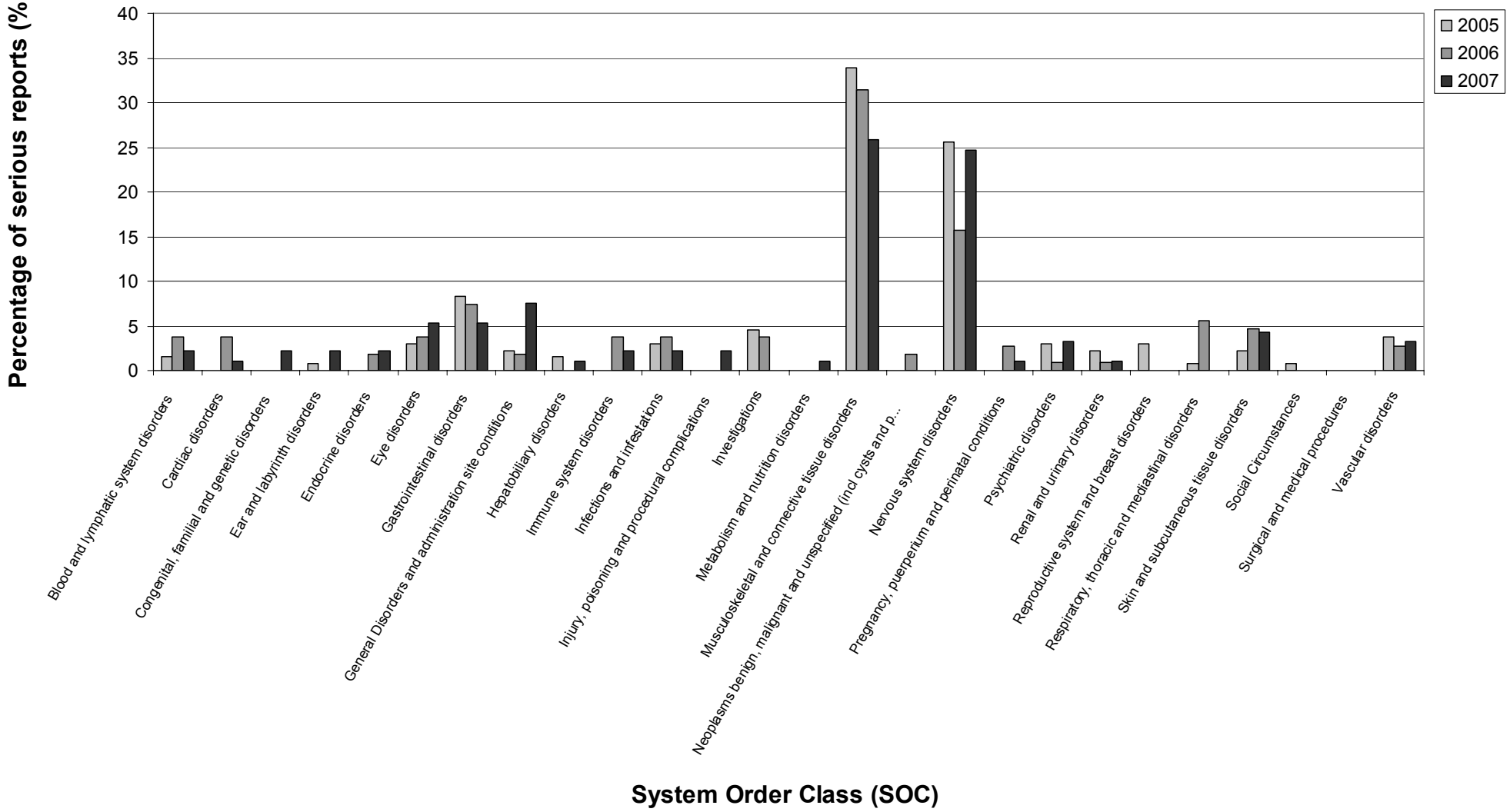
ERR = Estimated Reporting Rate
n/a Data not available at the time of writing this report.

The distribution data for the vaccine during 2007 were not available at the time of writing this report and as such, ERRs have not been calculated.

Figure 8 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 and convulsion.

Conclusion: No significant new safety issues have been identified during 2007.

Figure 8: Percentage of serious reactions per SOC associated with Hepatitis B vaccine



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 12). The number of reports received over this period has maintained relatively constant.

Table 12: Total number of Influenza reports and doses distributed (serious reports in brackets)

	2005	2006	2007
Total Number of Reports	139 (95)	138 (103)	125 (90)
Total Number of Reactions	320 (127)	417 (132)	349 (110)
Total Fatal	7 3		5
Exposure	14,000,000	14,000,000	14,000,000
ERR per 100,000 doses	0.8 (0.52)	0.8 (0.6)	0.9 (0.5)

ERR = Estimated Reporting Rate

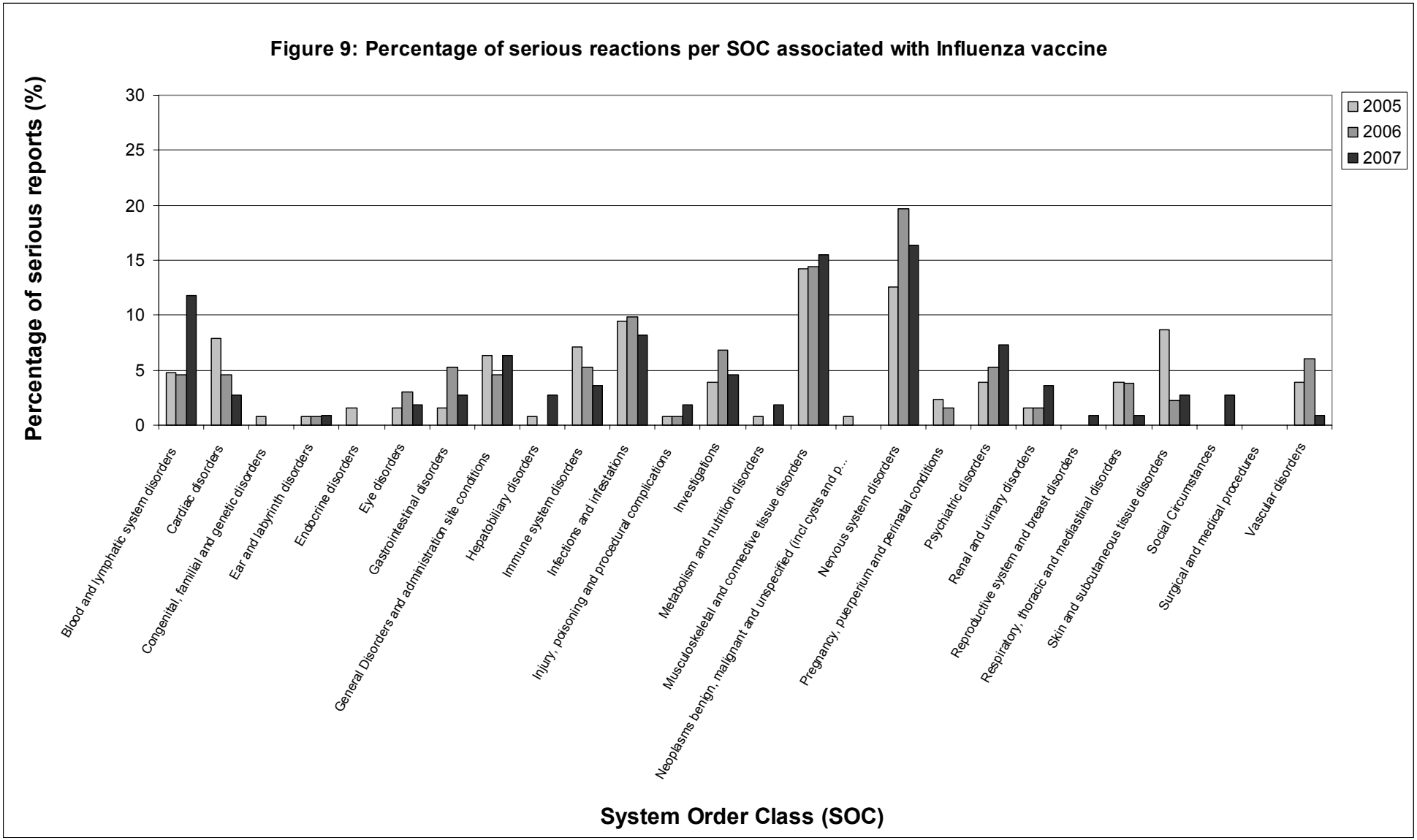
As in previous years, exposure has been estimated at 14m doses.

Figure 9 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 lymphadenopathy and arthralgia, which are recognised reactions.

There were five suspected ADRs with a fatal outcome in 2007. There were two cases of death unexplained, one case of sudden death, one case of myocardial infarction and one case of haemolytic anaemia. 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 2007.

Figure 9: Percentage of serious reactions per SOC associated with Influenza vaccine



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)

	2005	2006	2007
Total Number of Reports	233 (145)	128 (81)	93 (69)
Total Number of Reactions	587 (123)	392 (86)	287 (54)
Total Fatal	4	1	1
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.

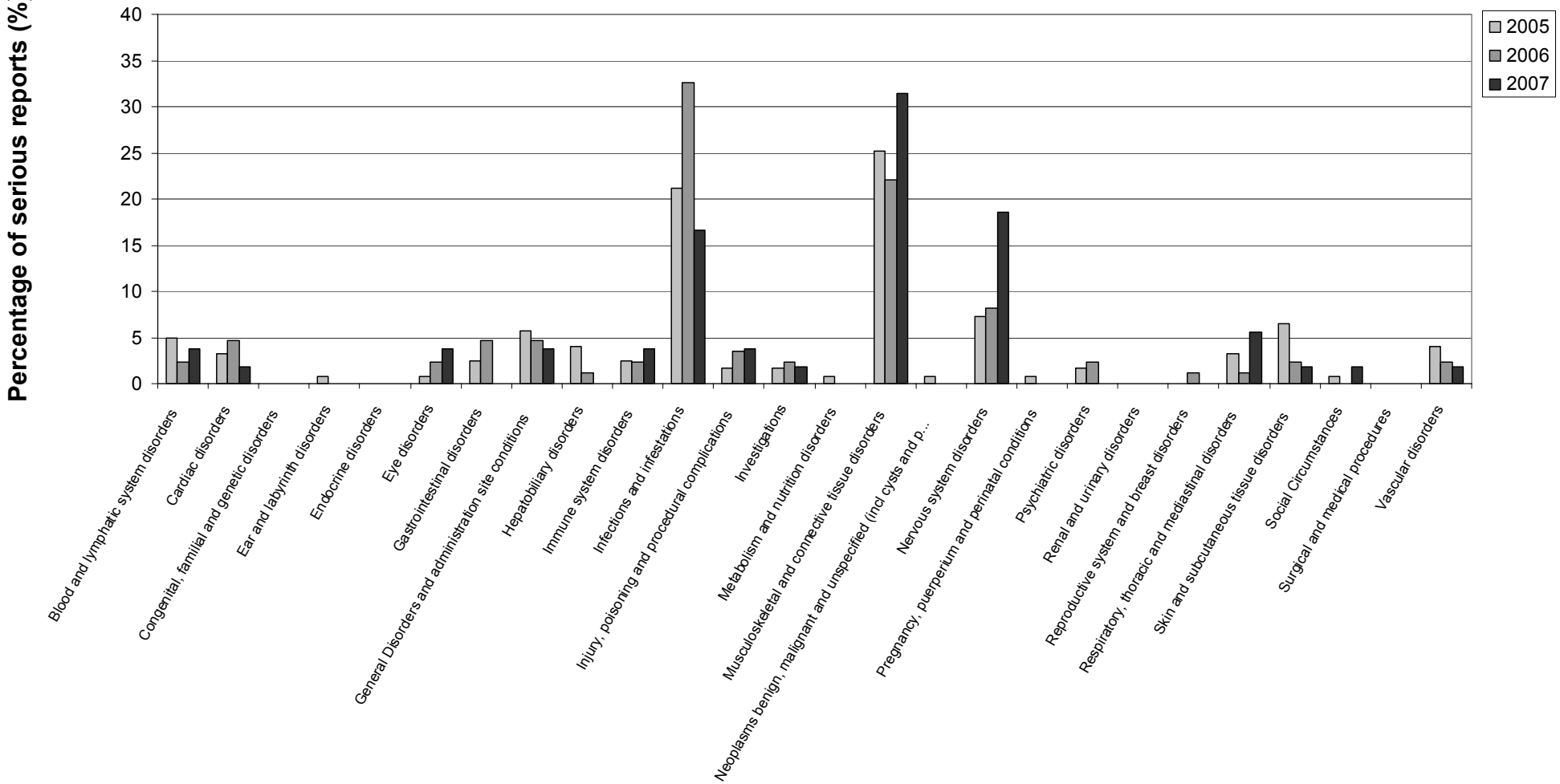
The distribution data for the vaccine during 2007 were not available at the time of writing this report and as such, ERRs have not been calculated.

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 for pneumococcal polysaccharide vaccine during 2007 was myalgia, followed by cellulitis and arthralgia (all of which are recognised reactions).

There was one fatal report of anaphylactic reaction reported during 2007.

Conclusion: No significant new safety issues have been identified during 2007.

Figure 10: 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)

	2005	2006	2007
Total Number of Reports	330 (109)	38 (18)	40 (25)
Total Number of Reactions	453 (45)	46 (11)	64 (24)
Total Fatal	0	1	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.

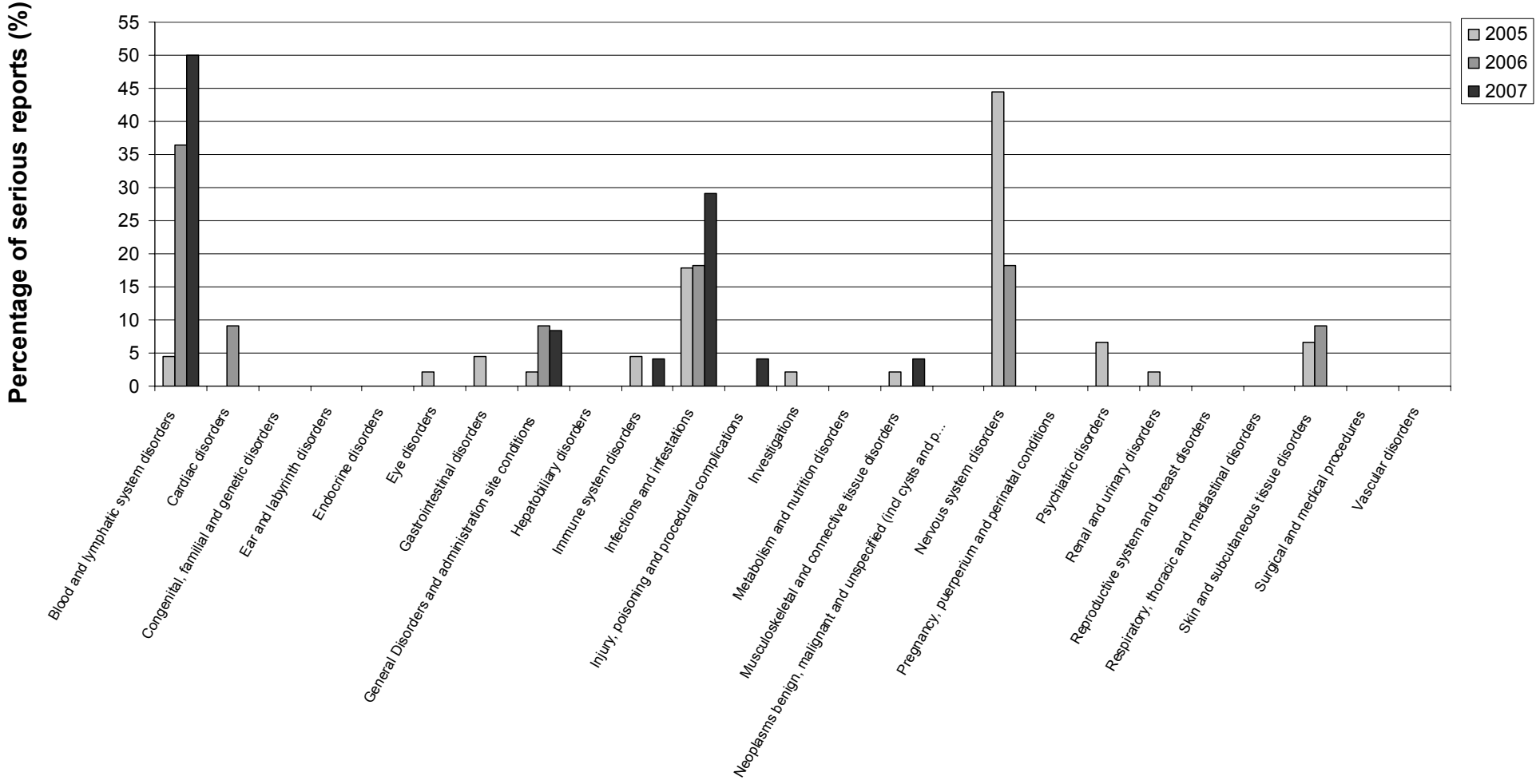
The distribution data for the vaccine during 2007 were not available at the time of writing this report and as such, ERRs have not been calculated.

Figure 11 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 these were mainly lymphadenitis and lymphadenopathy (both of which are recognised reactions). There were 4 reports of tuberculosis reported during 2007.

There were no fatal reactions reported during 2007.

Conclusion: No significant new safety issues have been identified during 2007.

Figure 11: 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 a nd Varilrix was first authorised in June 2002. The total num ber of suspected ADRs r eported 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)

	2005	2006	2007
Total Number of Reports	15 (6)	19 (11)	24 (17)
Total Number of Reactions	39 (6)	66 (17)	62 (25)
Total Fatal	0	1	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 th e vaccine during 2007 were not available at the tim e of writing this report and as such, ERRs have not been calculated.

The table below (Table 16) lists the serious ADRs reported in 2007 (note – one Yellow Card m ay contain m ore than one serious ADR). Seriousness is determ ined either by regulatory criteria or by reporter judgement.

Table 16: Serious reactions reported for Varicella Zoster Virus

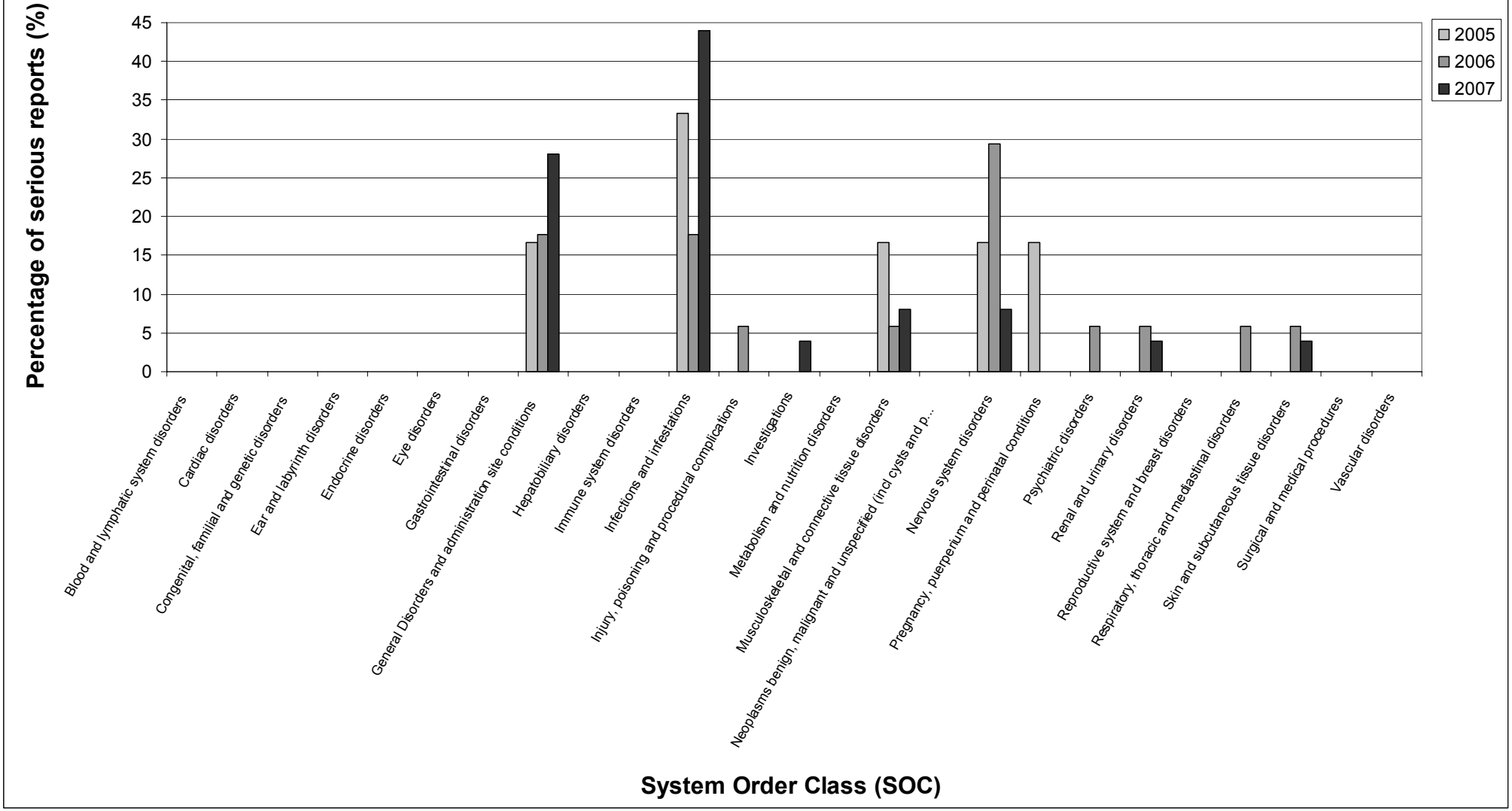
Reaction (PT)	Number of Reports
VACCINATION FAILURE	7
VARICELLA 10	
VARICELLA POST VACCINE	1
BLOOD CALCIUM INCREASED	1
MUSCULOSKELETAL CHEST PAIN	1
SYSTEMIC LUPUS ERYTHEMATOSUS	1
FACIAL PALSY	1
LOSS OF CONSCIOUSNESS	1
RENAL FAILURE	1
PSORIASIS 1	

The m ajority of seriou s rea ctions occurr ed within the 'General disorders and administration site conditions' SOC and the 'Infections and infestations' SOC. These were m ainly vaccinatio n failure (7 cases), varicella (10 cases) and v aricella post vaccine (1 case). F igure 12 shows the seri ous ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years.

There were no fatal reactions reported during 2007.

Conclusion: No significant new safety issues have been identified during 2007.

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



2. KEY ISSUES CONSIDERED BY CHM'S BIOLOGICALS AND VACCINES EXPERT ADVISORY GROUP (BVEAG) AND/OR ITS PHARMACOVIGILANCE EXPERT ADVISORY GROUP (PEAG) DURING 2007 AND TO DATE.

2.1 Update on Rotateq vaccine and Kawasaki's disease

RotaTeq and Rotarix are both authorised with in the EU but only RotaTeq is currently approved in the US. W ithin Europe, the UK is rapporteur for Ro taTeq and therefore directly responsible for monitoring its ongoi ng safety; Belgium is the rapporteur for Rotarix.

Because of previous ex perience with Rotash ield, pre-licens ing studies were design ed to identify an increased risk of intussusception. W hilst 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 b een identified as a po tential in assoc iation with RotaTe q but has not been confirm ed. Large post-marketing surveillance studies will further investigate a possible association with both intussusception and Kawasaki Disease. W e are not aware of any sa fety concerns with respect to Rotarix ; ho wever, Rotarix h as so far been used in countries whose Pharmacovigilance system s are likely to be less well developed than the US and Europe.