Paper provided by MHRA for
Joint Committee on Vaccination and Immunisation
June 2011:

VACCINE-ASSOCIATED SUSPECTED ADVERSE REACTIONS REPORTED VIA THE YELLOW CARD SCHEME DURING 2010

August 2011

CONTENTS

Introduction

This paper was prepared by the Medicines and Healthcare products Regulatory Agency (MHRA) for the October 2011 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 2010 to 31st December 2010.

Section 2 provides an update on vaccine safety issues considered by the Commission on Human Medicines (CHM) and/or its Expert Advisory Groups during 2010 and to date.

It should be noted that a report of a suspected 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.

The data contained in this report may therefore include some known side effects as well as purely coincidental events. For this reason, these data must not be considered as a list of known vaccine side effects. The recognised side effects of all vaccines are described in the product information (Summary of Product Characteristics [SPC] and Patient Information Leaflet [PIL). These are provided with the vaccine and are available for viewing on the electronic Medicines Compendium (eMC) website [http://emc.medicines.org.uk/].

Furthermore, due to variable levels of reporting and as the precise number of individuals immunised is not stated, the number of ADR reports received should not be used as a basis for estimating the incidence of ADRs or for comparing relative safety of vaccines. For some routine childhood vaccines, exposure estimates in this report are based on 2009/10 uptake data[1], extrapolated to the UK birth cohort. Exposure for non-routine vaccines has not been estimated. As the reporting rates are broad estimates, as they do not take into account exposure outside of the routine schedule and are not adjusted for age-specific exposure, no firm conclusions can be drawn on relative ADR reporting rates over time.

Yellow Card reports may contain more than one serious ADR. Seriousness is determined by regulatory criteria based on the medical condition (MedDRA Dictionary serious)[2]. Yellow Card data covers the whole of the UK.

Prepared: August 2011

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

[1] http://www.ic.nhs.uk/webfiles/publications/003_Health_Lifestyles/immstats0910/Immunisations_Bulletin_2009-10.pdf
[2] MedDRA - the Medical Dictionary for Regulatory Activities - is a standardised, medically validated adverse event terminology system used within the international medicines regulatory environment.

1. YELLOW CARD DATA

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 was 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 3 years is shown below (table 1). 2010 exposure is based on the assumption of 90% uptake (one dose) for an annual birth cohort of 760,000[3].

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

	2008	2009	2010
Total number of reports	48 (12)	26 (9)	27 (13)
Total number of reactions	105 (21)	67 (11)	74 (18)
Total fatal	2	0	0
Exposure (doses)	585,000	630,000	684,000
ERR per 100,000 doses	8.2 (2.1)	4.1 (1.4)	3.9 (1.9)

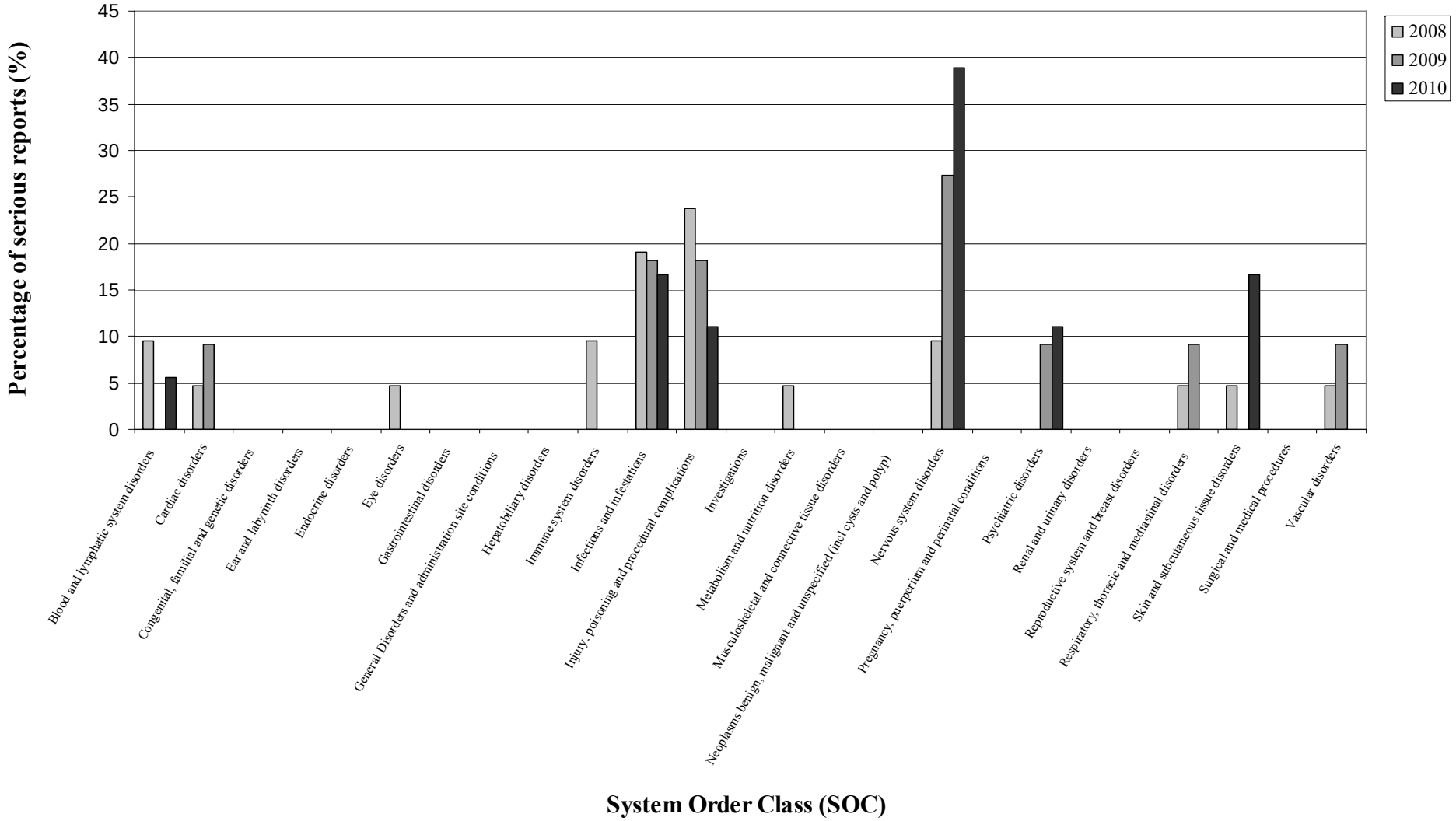
ERR = Estimated Reporting Rate

Figure 1 shows the serious ADRs reported in each MedDRA System Organ Class (SOC), as a percentage of the total ADRs, for the last three years. These are based on small numbers. The majority of the serious ADRs reported for Menitorix vaccine in 2010 belonged to the 'Nervous System Disorders' SOC, the majority of which were reports of 'Febrile Convulsion' (4 cases). This was followed by the 'Infections and Infestations' and the 'Skin and subcutaneous tissue disorders' SOCs. However, in all cases, numbers of reports were very small.

Conclusion: No significant new safety issues were identified during 2010.

[3] http://www.ons.gov.uk

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



1.1.2. Prevenar 13▼ (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 12 to 13 months of age. Prior to UK introduction, there was substantial international experience in the safety of pneumococcal conjugate vaccine.

In April 2010 Prevenar vaccine, which contained antigens against seven pneumococcal strains, was replaced by Prevenar 13, which contains antigens against 13 strains, to broaden protection against pneumococcal disease. This new vaccine is currently being monitored on the black triangle intensive monitoring scheme. 2010 exposure is based on the assumption of 93% uptake for primary doses and 87% uptake for booster dose for an annual birth cohort of 760,000.

The total number of suspected ADRs reported in association with pneumococcal conjugate vaccine over the last 3 years is shown below (table 2).

Table 2: Total number of Prevenar reports (serious reports in brackets)

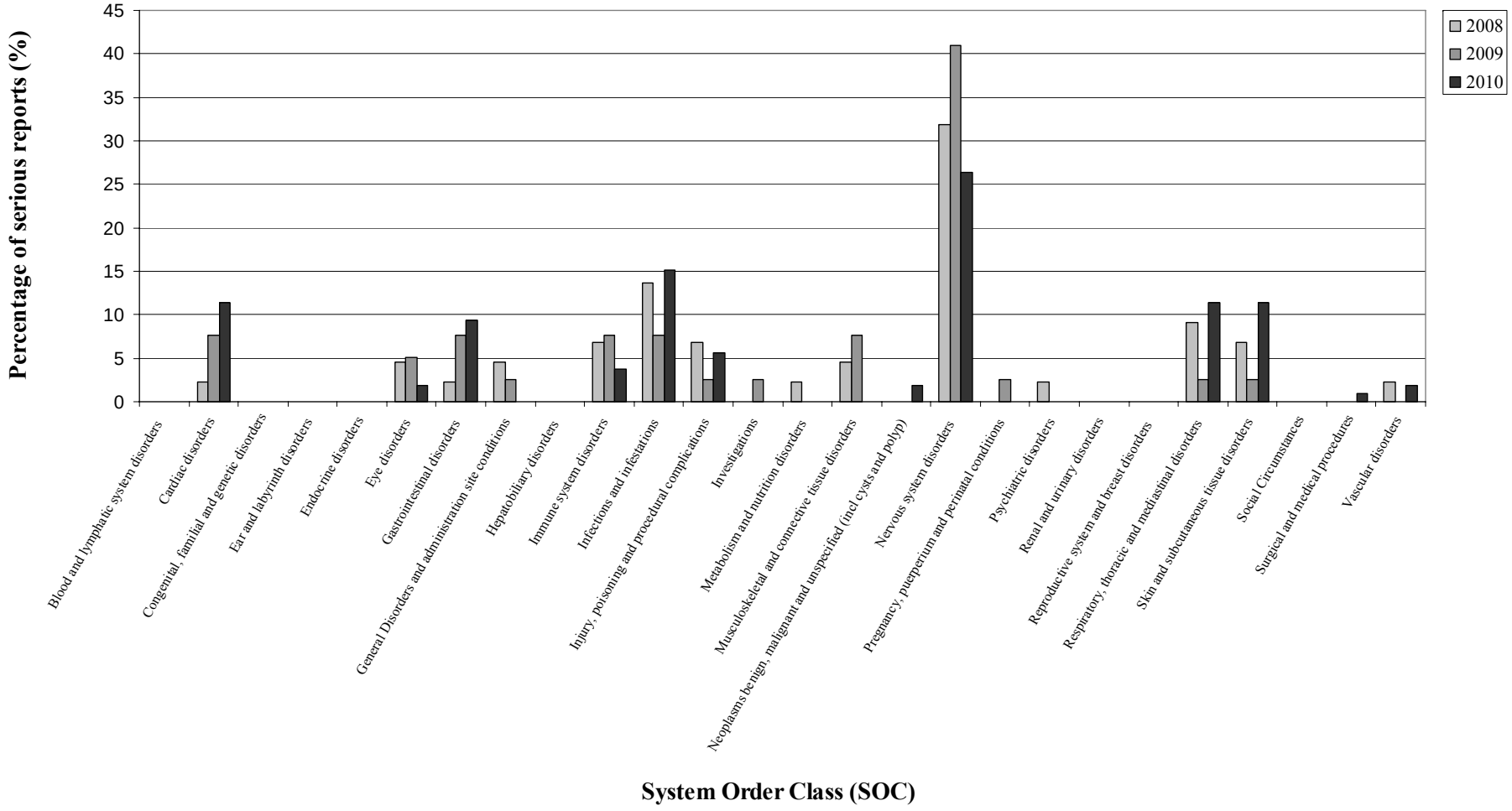
	2008	2009	2010
Total number of reports	146 (37)	86 (27)	91 (35)
Total number of reactions	325 (44)	218 (39)	253 (53)
Total fatal	3	3	0
Exposure (doses)	1,800,000	1,900,000	2,074,800
ERR per 100,000 doses	8.1 (2.1)	4.5 (1.4)	4.4 (1.7)

ERR = Estimated Reporting Rate

Figure 2 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. Although it remains the highest reported SOC, since last year there has been a decrease in the percentage of serious reactions reported in the 'Nervous system disorders' SOC. The most reported serious reaction from this SOC is relating to 'convulsions' (5 cases - 2 of 'Convulsion', 2 of 'Febrile Convulsion' and 1 of 'Petit Mal Convulsion'), followed by 'Unresponsive to Stimuli' (4 cases), and 'Hypotonia' (2 cases). Seizures (including febrile) are rare recognised adverse reactions to the vaccine.

Conclusion: No significant new safety issues were identified during 2010. Based on experience in the UK and across the EU, the safety profile of Prevenar 13 is considered to be equivalent to that of Prevenar.

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



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

Pediacel is the routine DTPa/IPV/Hib vaccine, administered at 2, 3 and 4 months of age.

Infanrix IPV Hib (DTaP IPV Hib) vaccine was used from September 2007 to March 2009 as part of a Haemophilus influenzae type B (Hib) catch-up campaign as a pre-school booster. This accounted for the increased number of reports in 2008/9 (note: exposure in 2008/9 was based only on DTPa/IPV/Hib vaccine as a 3 dose primary course since estimates on exposure to Infanrix IPV Hib were not available).

No Infanrix IPV Hib cases have been received since 2009.

The total number of suspected ADRs reported in association with DTPa/IPV/Hib for the last 3 years is shown below (table 3). 2010 exposure is based on the assumption of 95% uptake (3 doses) for an annual birth cohort of 760,000.

Table 3: Total number of DTaP/IPV/Hib vaccine reports and doses distributed (serious reports in brackets)

	2008	2009	2010
Total number of reports	262 (60)	122 (40)	64 (29)
Total number of reactions	581 (85)	314 (66)	187 (46)
Total fatal	5	1	0
Exposure (doses)	2,000,000	1,950,000	2,166,000
ERR per 100,000 doses	13.1 (3.0)	6.3 (2.1)	2.9 (1.3)

ERR = Estimated Reporting Rate

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

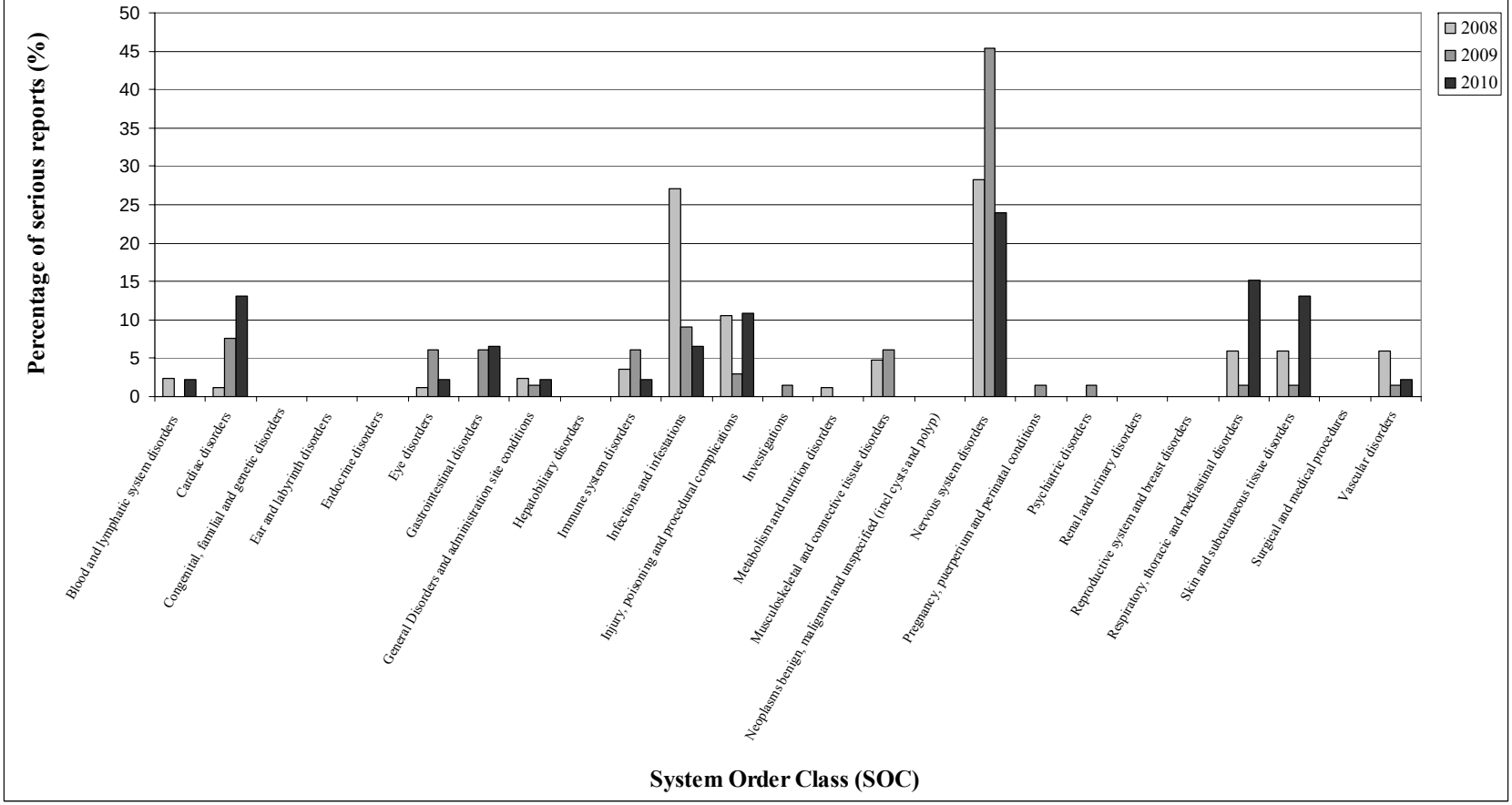
Approximately 24% of serious ADRs were from the 'Nervous System Disorders' SOC and largely consisted of reports of 'Unresponsive to Stimuli' and 'Convulsion' reactions (hypotonic hyporesponsive episodes and febrile convulsions are recognised reactions). This was a decrease from 45% of all ADRs last year.

There was an increase in the percentage of reactions in the 'Respiratory, Thoracic and Mediastinal Disorders' SOC; these included 2 reports of 'Respiratory Arrest' and 2 cases of apnoeic events (one 'Apnoea' and one 'Apnoeic Attack'). Apnoea in premature infants is a recognised reaction; both respiratory arrest cases were in association with a hypotonic hyporesponsive episode.

There was also an increase in the percentage of reactions in the 'Skin and Subcutaneous Tissue Disorders' SOC; the majority of these were related to allergic reactions to the vaccine (2 cases of 'Swelling Face', one case of 'angioedema') which are recognised adverse reactions.

Conclusion: No significant new safety issues were identified during 2010.

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



1.1.4. MMR vaccine

The first routine childhood dose of MMR vaccine is administered at 12-13 months of age, with a second dose from 3 years 4 months.

.The total number of suspected ADRs reported in association with MMR vaccination for the last 3 years is shown below (table 4). 2010 exposure is based on the assumption of 89% uptake for dose 1 and 83% for dose 2 for an annual birth cohort of 760,000. Note: the exposure estimates are based on only routine childhood use and do no estimate usage in older age groups, or use in catch-up campaigns. Exposure is therefore an underestimate.

Table 4: Total number of MMR vaccine reports and doses distributed (serious reports in brackets)

	2008	2009	2010
Total number of reports	124 (67)	145 (72)	124 (65)
Total number of reactions	311 (93)	431 (113)	405 (123)
Total fatal	1	3	1
Exposure (doses)	1,105,000	1,204,000	1,307,200
ERR per 100,000 doses	11.2 (6.1)	12.0 (5.9)	9.5 (4.9)

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.

The 'Nervous System Disorders' SOC has the highest percentage of serious reactions over the last three years. An increase to 28% of all serious reactions reported was seen in 2010, compared to 14% in 2009. The majority of the reactions related to loss of consciousness and syncope (6 'Syncope', 4 'Loss of Consciousness', 2 'Hypotonia' and 2 'Unresponsive to Stimuli'). 11 cases relating to convulsions were also reported in 2010 (6 'Febrile Convulsion', 2 'Convulsion', 2 'Petit Mal Epilepsy' and 1 case of 'Epilepsy'). Syncope and convulsions are listed for the MMR vaccines.

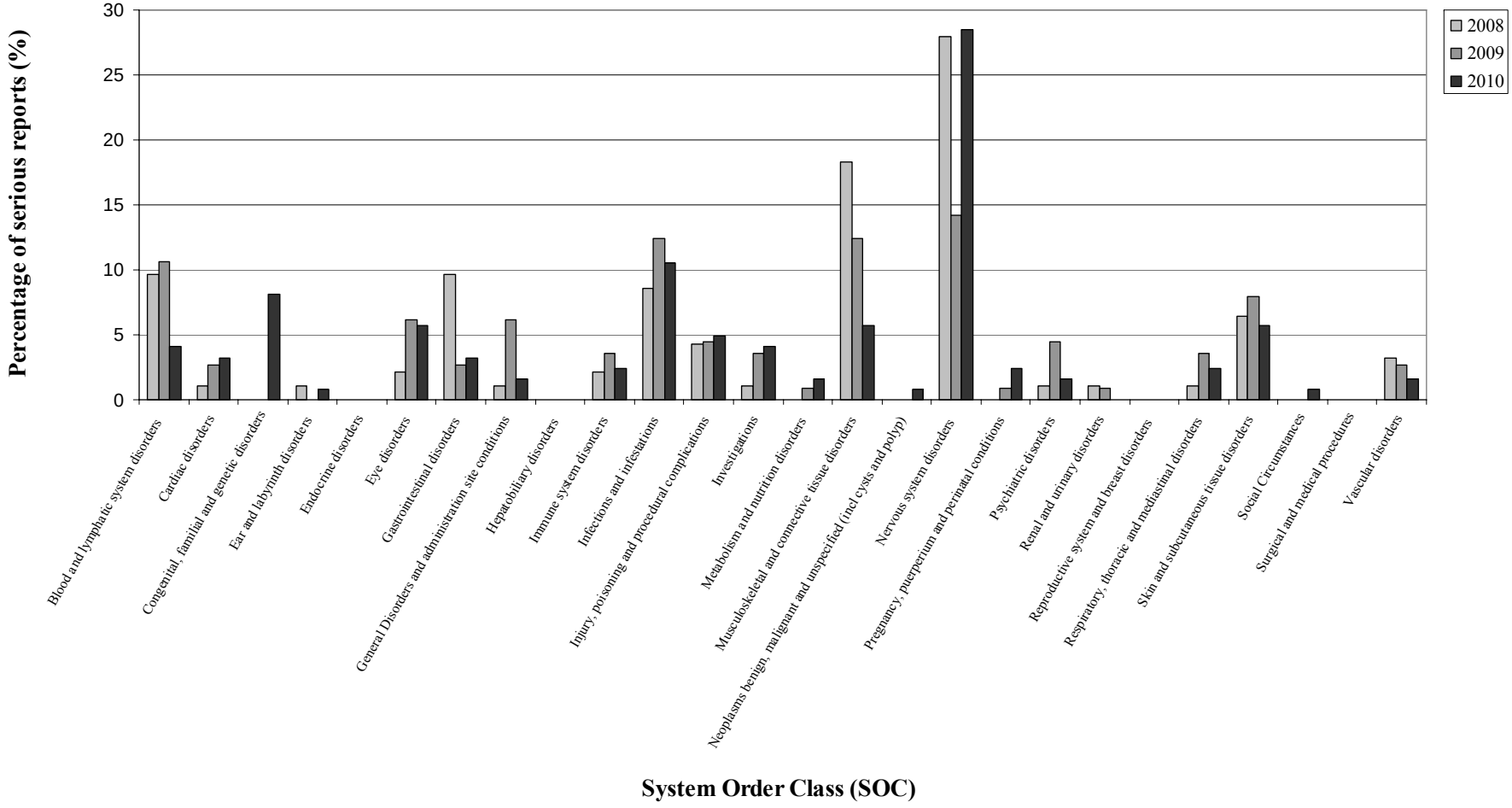
The percentage of serious reactions reported in the 'Congenital Disorders' SOC increased from 0% in 2008 and 2009 to 10% in 2010. The 10 reactions contained in this SOC all originate from a single case.

The proportion of serious reactions in the 'Musculoskeletal and Connective Tissue Disorders' SOC has declined over the last three years to 6% of all serious reactions reported in 2010, compared with 18% in 2008.

One fatal report of 'Encephalitis' was received during 2010. A causal association with this fatal event has not been established.

Conclusion: No significant new safety issues were identified during 2010.

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



1.1.5. Meningitis C vaccine

Meningococcal group C conjugate vaccine is recommended for use at 3 and 4 months of age as a primary course (2 dose schedule) (with a MenC/Hib booster at 12-13 months).

The total number of suspected ADRs reported in association with Meningococcal group C conjugate vaccine for the last 3 years is shown below (table 5). 2010 exposure is based on the assumption of 93% uptake (2 doses) for an annual birth cohort of 760,000.

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

	2008	2009	2010
Total number of reports	54 (16)	44 (13)	49 (24)
Total number of reactions	124 (29)	93 (21)	133 (46)
Total fatal	2	0	1
Exposure (doses)	1,170,000	1,290,000	1,413,600
ERR per 100,000 doses	4.6 (1.4)	3.4 (1.0)	3.5 (1.7)

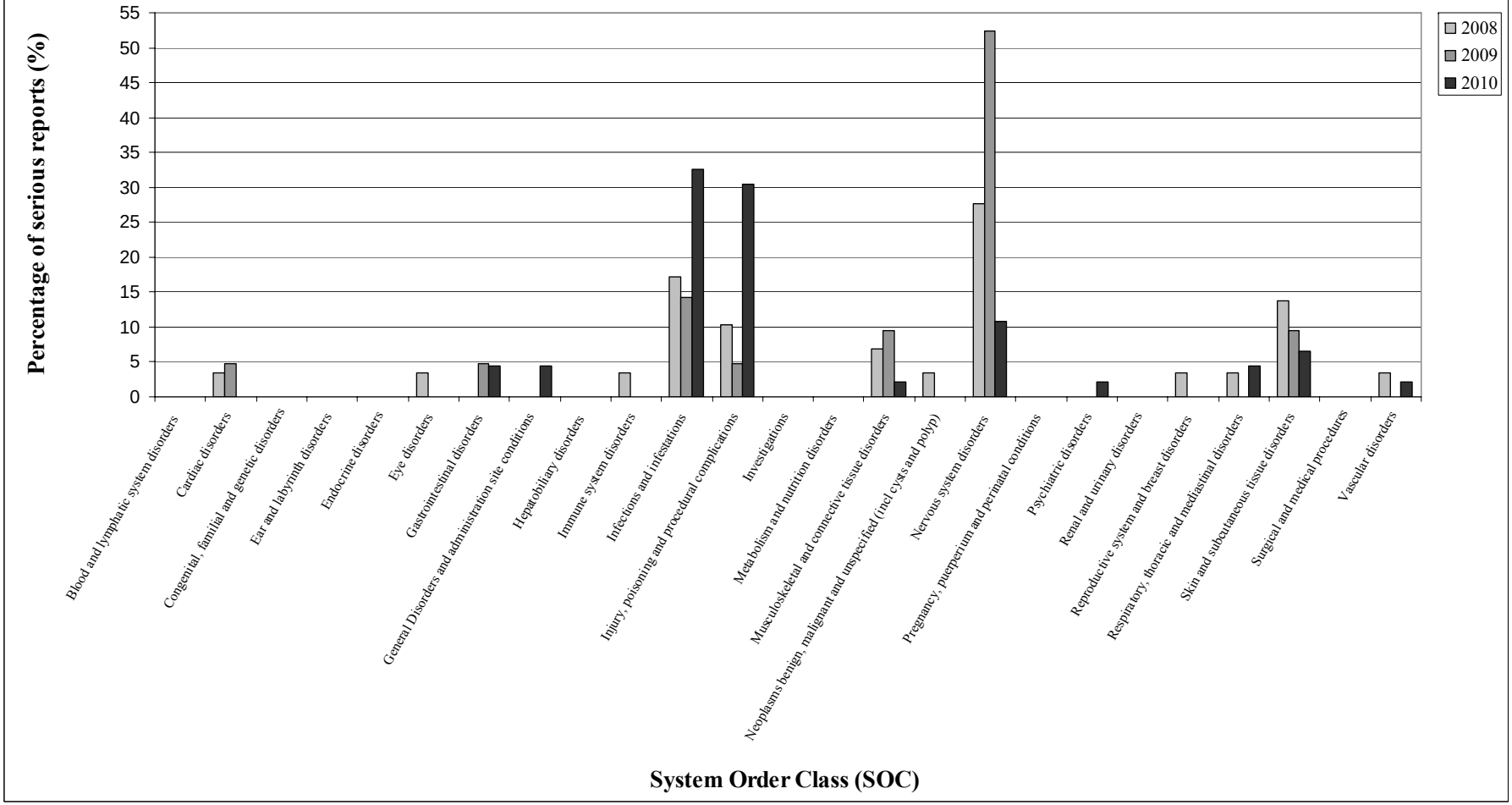
ERR = Estimated Reporting Rate

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 'Infections and Infestations' SOC, which had a large increase in cases from 2009, with the most reported serious reactions in this SOC being 'Meningitis Meningococcal' (8 reports) and 'Meningococcal Infection' (3 reports). Two of these cases were received from the Health Protection Agency, and the others were derived from a literature article concerning vaccination of patients with functional T cell deficiency[4]. The 'Injury, Poisoning and Procedural Complications' SOC had the second largest proportion of serious reactions and also showed a large increase in cases from the previous year; the highest proportion of these cases were reports of 'Vaccination Failure', in association with the meningococcal infections experienced in the Infections SOC.

Conclusion: No significant new safety issues were identified during 2010.

[4] Foster RA et al, Functional T-Cell Deficiency in Adolescents Who Experience Serogroup C Meningococcal Disease despite Receiving the Meningococcal Serogroup C Conjugate Vaccine. Clin Vaccine Immunol. 2010 July; 17(7): 1104–1110

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



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

Infanrix IPV or Repevax is recommended as a routine pre-school booster vaccine.

The total number of suspected ADRs reported in association with d/DTaP/IPV vaccine for the last 3 years is shown below (table 6). The exposure rate for Repevax and Infanrix IPV were not calculated for 2008 or 2009 as these vaccines were not routinely used due to use of DTaP/IPV/Hib as pre-school booster during the Hib catch-up campaign. Reversion back to Infanrix IPV Hib/Repevax explains the increase in reports received in 2010. 2010 exposure is based on the assumption of 85% uptake (1 dose) for an annual birth cohort of 720,000 (2007 birth cohort).

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

	2008	2009	2010
Total number of reports	10 (2)	30 (5)	68 (18)
Total number of reactions	28 (7)	69 (10)	185 (32)
Total fatal	0	0	0
Exposure (doses)	n/a	n/a	612,000
ERR per 100,000 doses	n/a	n/a	11.1 (2.9)

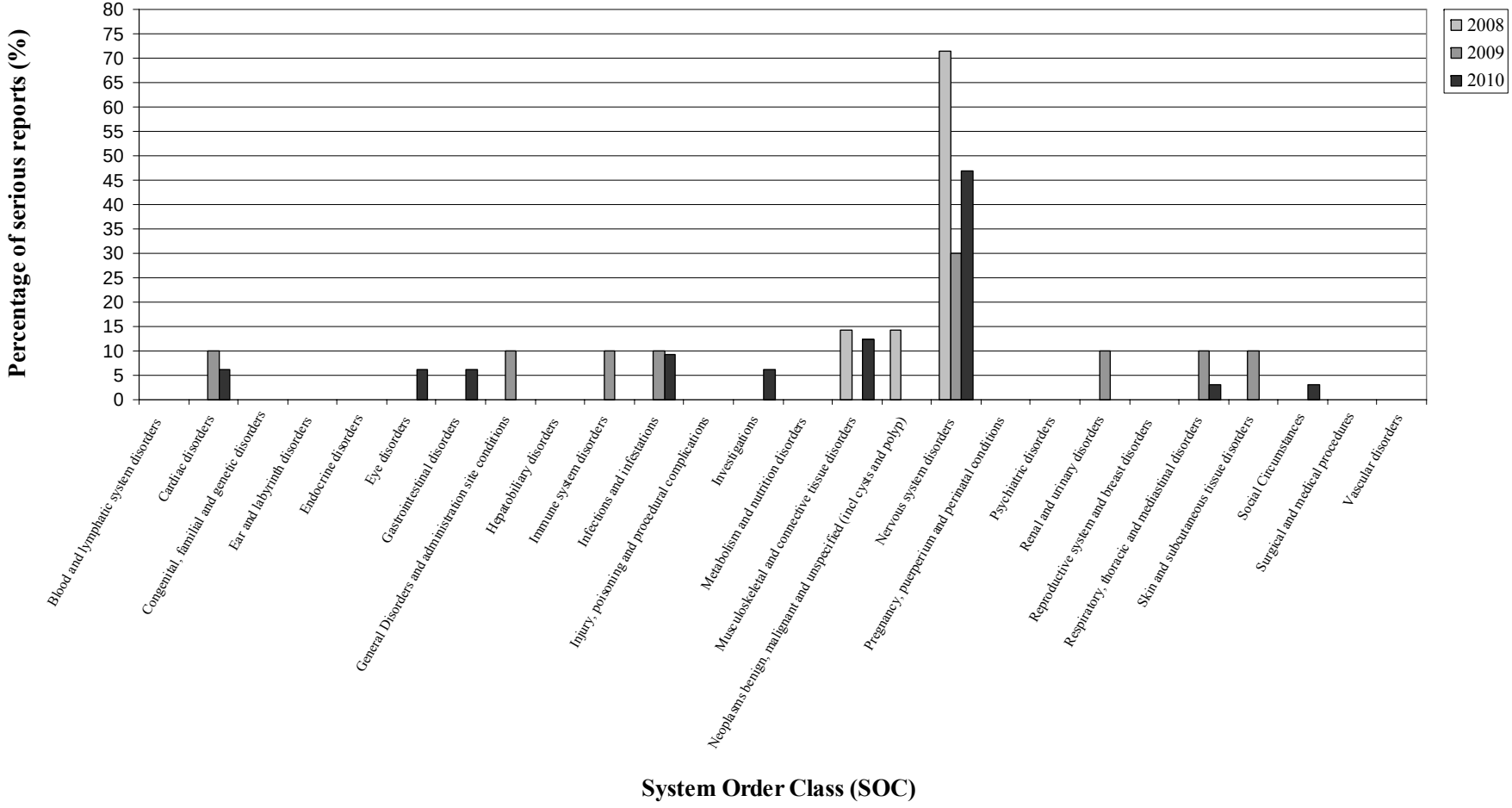
ERR = Estimated Reporting Rate

Figure 6 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. The majority of reactions reported in this SOC were in association with syncope or depressed consciousness levels (4 'Syncope', 2 each of 'Loss of Consciousness', 'Unresponsive to Stimuli' and 'Hypotonia', and 1 case of 'Depressed Level of Consciousness'). The SPC for this vaccine lists vasovagal syncope and convulsions.

Conclusion: No significant new safety issues have been identified during 2010.

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, as well as being used 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 7).

Based on uptake data, it estimated that at least 450,000 doses of Revaxis were administered to those aged 13-18 years in 2010 – however, this is likely to be an underestimate[1]. Furthermore, there is also likely to be significant usage in older age groups (e.g. tetanus boosters, travel vaccination). An estimate of exposure is therefore not attempted in this paper.

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

	2008	2009	2010
Total number of reports	81 (44)	102 (60)	92 (43)
Total number of reactions	256 (74)	387 (118)	279 (70)
Total fatal	2	0	0
Exposure (doses)	n/a	n/a	n/a
ERR per 100,000 doses	n/a	n/a	n/a

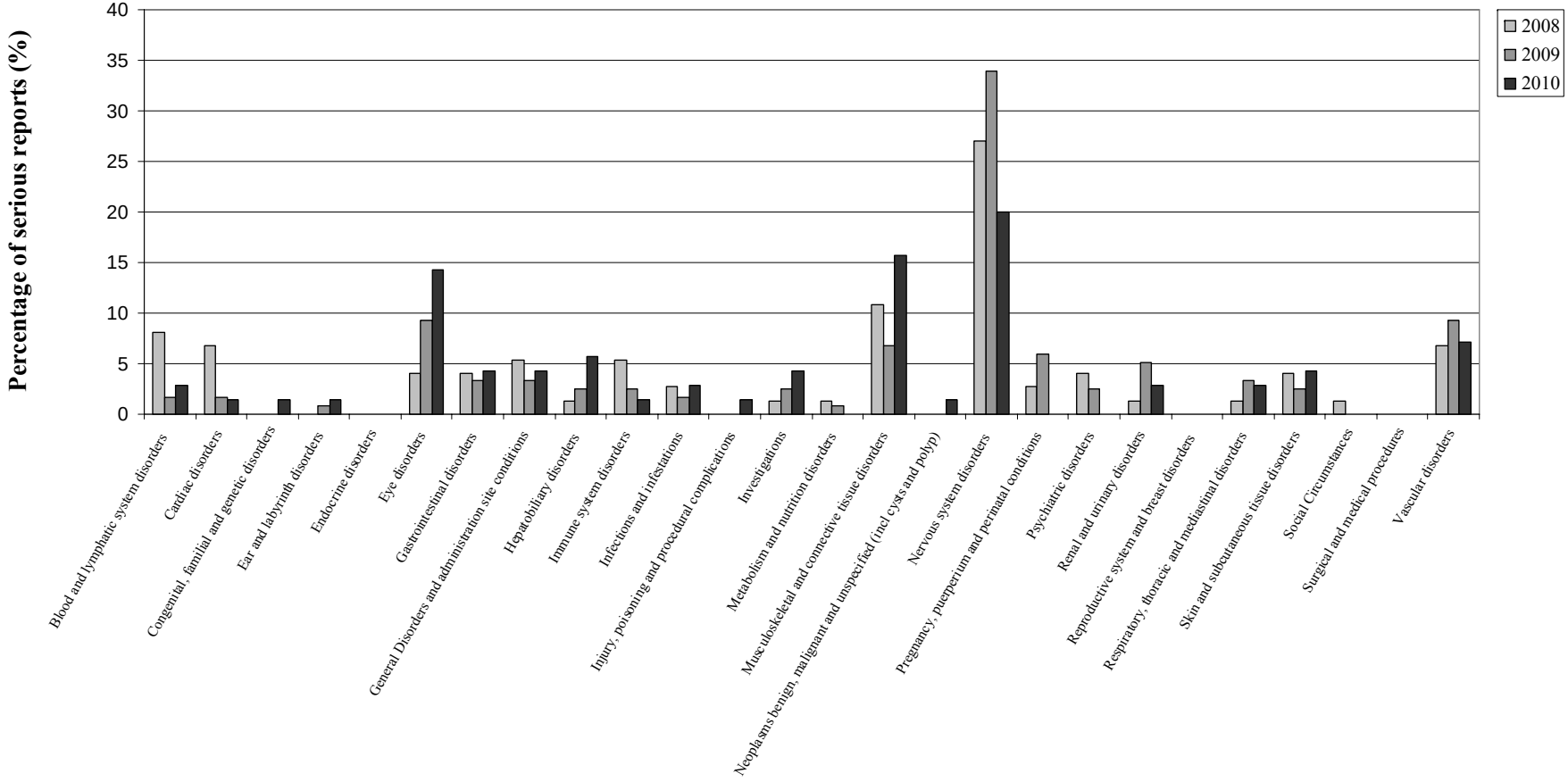
ERR = Estimated Reporting Rate
n/a: Data not available at the time of writing this report.

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, comprising 20% in 2010. This compares to 34% of all serious reactions reported in 2009. Most reports in this SOC were due to fainting. We received 3 reports of 'Syncope' and 3 reports of 'Loss of Consciousness'.

The proportion of serious reactions in the 'Eye Disorders' SOC increased to 14% in 2010; the majority of these reactions were 'Eye Swelling' (4 reports) and 'Ocular Hyperaemia' (2 reports). The proportion of reactions in the 'Musculoskeletal and Connective Tissue Disorders' SOC also increased to 16% in 2010; the majority of these reactions were 'Musculoskeletal Stiffness' (4 reports) and 'Muscle Rigidity' (2 reports). The percentage increase in the proportion of serious cases in other SOCs is a result of the decrease of proportion of reports in the 'Nervous System Disorders' SOC.

Conclusion: No significant new safety issues have been identified during 2010.

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



1.1.8. Human Papillomavirus vaccines (Cervarix and Gardasil▼)

A routine immunisation programme for human papillomavirus (HPV) was started across the UK in September 2008 for 12 to 13 year-old girls. This also included a catch-up campaign for older teenagers. The vaccine of choice in the UK was Cervarix, which protects against infection with HPV types 16 and 18.

On introduction of the vaccine, the MHRA put in place a proactive pharmacovigilance strategy to monitor the safety of Cervarix vaccine as it was used in the UK. After use of more than 4.5 million doses of Cervarix in the UK alone, MHRA reverted to routine pharmacovigilance in 2010. The Commission on Human Medicines advised that no serious new risks have been identified in association with Cervarix and the balance of risks and benefits of the vaccine remains positive.

Further information regarding HPV vaccine, including MHRA's public safety assessment report on the first two years of the HPV immunisation programme, can be found on the MHRA website at www.mhra.gov.uk/HPVvaccine.

The total number of suspected ADRs reported in association with human papillomavirus vaccine for the last 3 years is shown below (table 8).

Table 8: Total number of Human Papillomavirus vaccine reports (serious reports in brackets)

	2008	2009	2010
Total number of reports	1327 (292)	1934 (614)	1802 (398)
Total number of reactions	2871 (371)	4776 (826)	3798 (560)
Total fatal	2	1	0

Two suspected ADRs with a fatal outcome were reported for Cervarix, however one case was due to underlying infection with Streptococcal A septicaemia and the other was due to the presence of a malignant tumour. Neither case was related to the vaccination. One fatal case was reported for Gardasil vaccine. This was a case of stillbirth in a 23 week old foetus. A causal association with vaccination has not been established.

Overall ADR reports relative to usage (from September 2008 to July 2010) is summarised in figure 8 below:

Figure 8: HPV ADR reports relative to usage

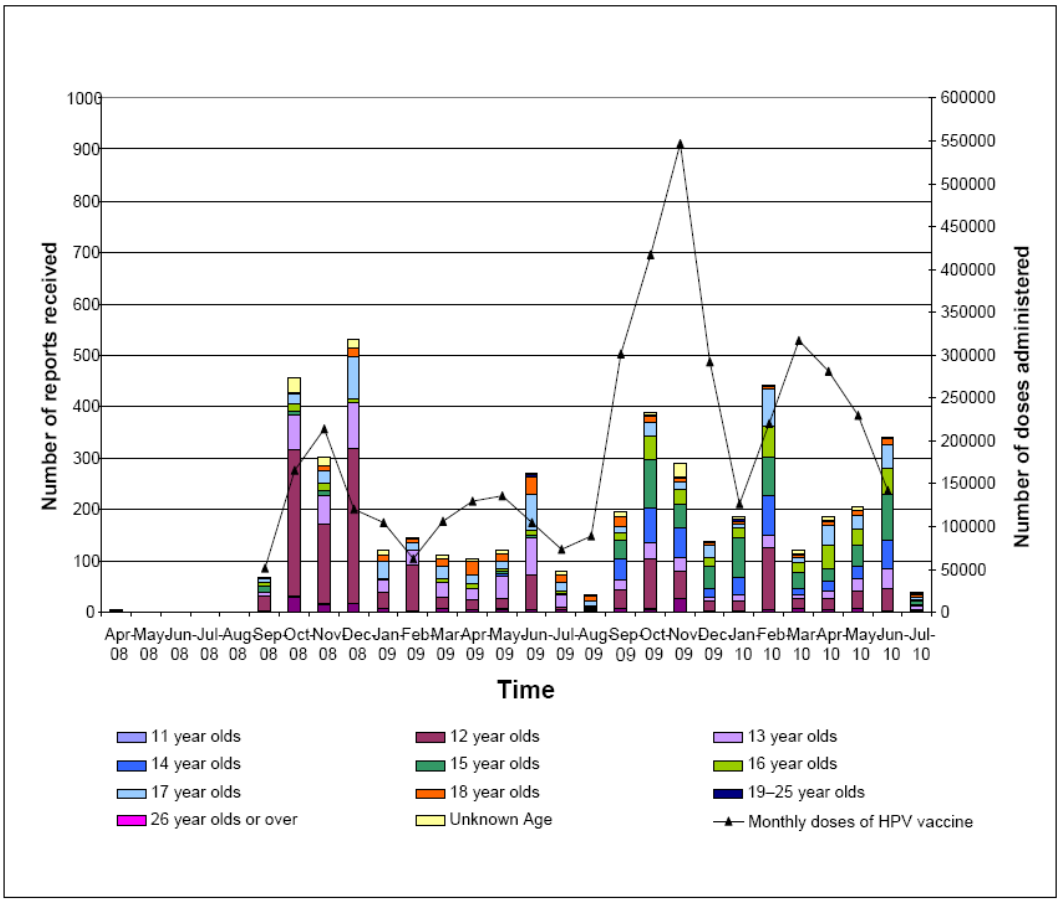
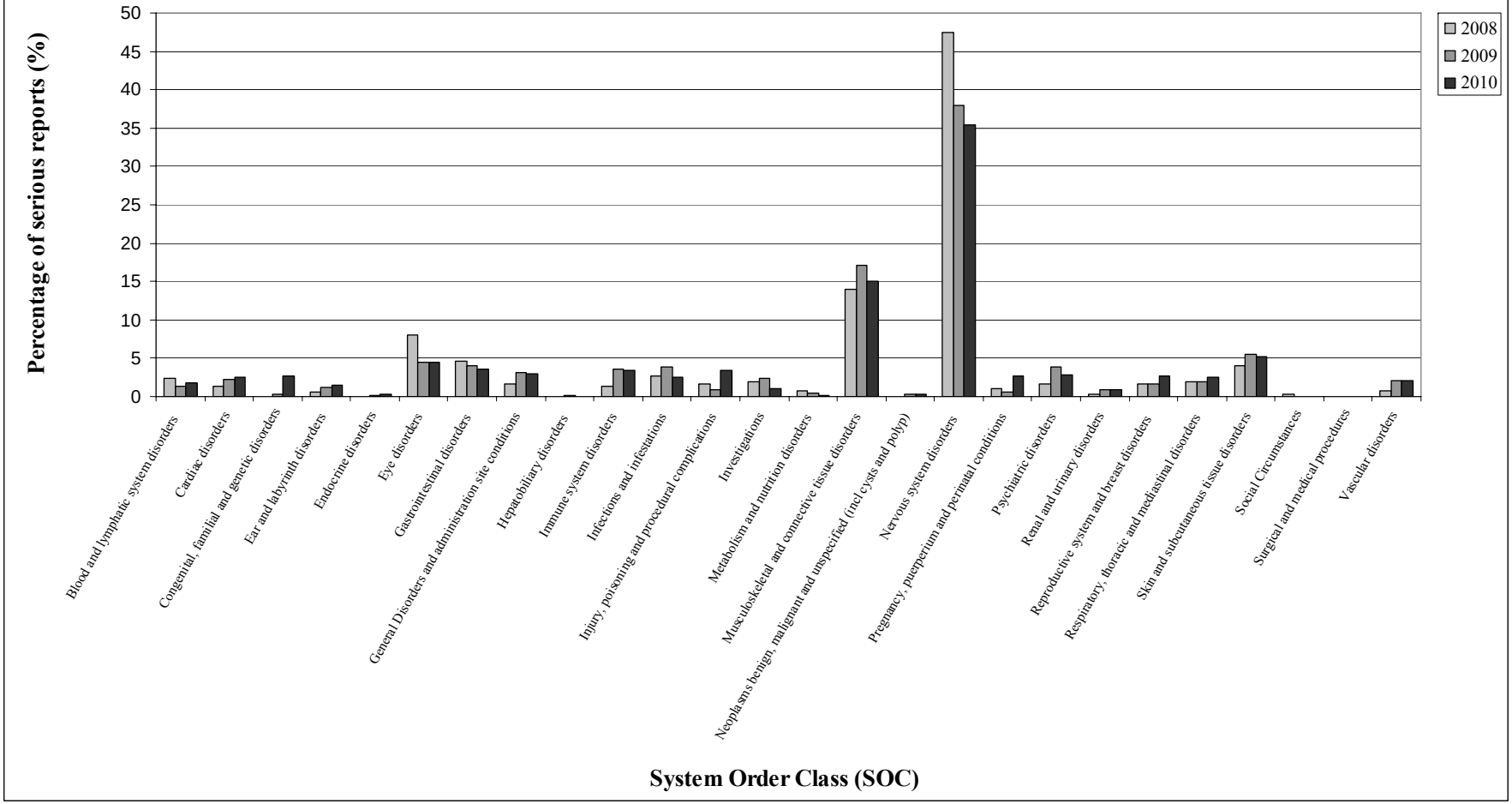


Figure 9 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years.

The majority of serious reactions occurred within the 'Nervous System Disorders' SOC and the 'Musculoskeletal and Connective Tissue Disorders' SOC. These were mainly 'Syncope' (faint) (113 cases) and 'Myalgia' (21 cases). The majority of all suspected adverse reactions reported related to signs and symptoms of either recognised/known adverse reactions that are listed in the product information or fainting episodes related to the procedure of vaccination.

Conclusion: No significant new safety issues have been identified during 2010.

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



1.2 Other vaccines

1.2.1. Hepatitis B vaccine

Hepatitis B vaccine is recommended in populations deemed to be at risk of contracting the disease.

The total number of suspected ADRs reported in association with single hepatitis B vaccine for the last 3 years is shown below (table 9).

Table 9: Total number of Hepatitis B vaccine reports and doses distributed (serious reports in brackets)

	2008	2009	2010
Total number of reports	106 (70)	104 (63)	77 (41)
Total number of reactions	398 (129)	385 (120)	181 (61)
Total fatal	1	1	0
Exposure (doses)	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.

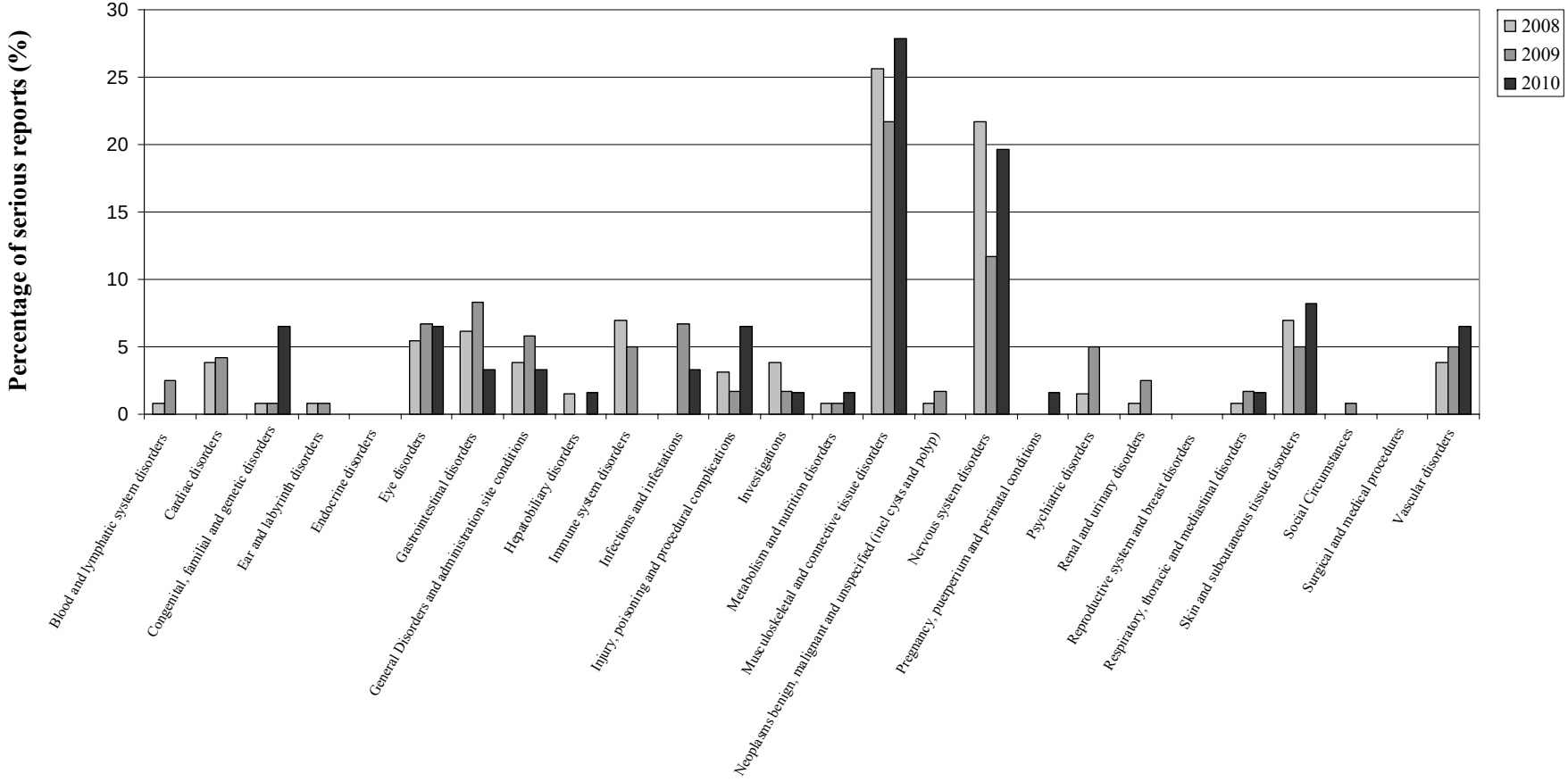
Estimated exposure data for the vaccine were not available at the time of writing this report and as such, ERRs have not been calculated.

Figure 10 shows the serious ADRs reported in each SOC, as a percentage of the total 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 'Myalgia' (5 cases) and 'Convulsion' (3 cases). These are both listed reactions for hepatitis B vaccine.

The proportion of reactions in the 'Congenital, Familial and Genetic Disorders' SOC increased to 7% in 2010 from 1% in 2008 and 2009. All the reactions reported in this SOC were derived from a single case.

Conclusion: No significant new safety issues have been identified during 2010.

Figure 10: Percentage of serious reactions per SOC associated with Hepatitis B vaccine



1.2.2. Seasonal Influenza Vaccine

Influenza vaccine is offered to at-risk populations in the community on a yearly basis, including the elderly and those at increased risk of complications of influenza infection[5].

The total number of suspected ADRs reported in association with seasonal influenza vaccine for the last 3 years is shown below (table 10). In line with the other data in this report, this relates to calendar years (rather than influenza seasons). As in previous years, exposure has been estimated simply at an upper level of 14m doses.

The increase in ADR reports over 2009 and 2010 is most likely accounted for by increased reporting due to concurrent administration of seasonal influenza vaccine and swine flu vaccine over the pandemic period, and use of the MHRA's 'swine flu ADR Portal' during the pandemic period.

Over the pandemic period, the MHRA had in place a separate proactive pharmacovigilance programme to monitor the safety of the new pandemic influenza (H1N1) vaccines, Pandemrix and Celvapan, as they were used in the UK. It is estimated that over 6million individuals were vaccinated over the 2009-2010 'flu season. The final public assessment report of all UK reports of suspected adverse reactions to the pandemic influenza vaccines is available at www.mhra.gov.uk/swineflu.

Table 10: Total number of Influenza reports and doses distributed (serious reports in brackets)

	2008	2009	2010
Total number of reports	116 (66)	209 (115)	323 (184)
Total number of reactions	322 (109)	691 (202)	1019 (283)
Total fatal	4	7	5
Exposure (doses)	14,000,000	14,000,000	14,000,000
ERR per 100,000 doses	0.8 (0.5)	1.5 (0.8)	2.3 (1.3)

ERR = Estimated Reporting Rate

Figure 11 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. The distribution of adverse reactions has stayed relatively constant over the last three years, with the majority of serious reactions occurred within the 'Nervous System Disorders' SOC and the 'Musculoskeletal and Connective Tissue Disorders' SOC. The most reported serious reactions in the 'Nervous System Disorders' SOC were 'Syncope' (9 cases), 'Convulsion' (6 cases), 'Guillain-Barre Syndrome' and 'Loss of Consciousness' (6 cases of each), and in the 'Musculoskeletal and Connective Tissue Disorders' SOC were 'Myalgia' (19 cases), and 'Arthralgia' (15 cases). Some of these reports may have been associated with seasonal and pandemic influenza vaccines rather than solely seasonal influenza vaccine, due to co-administration of the vaccines during the pandemic.

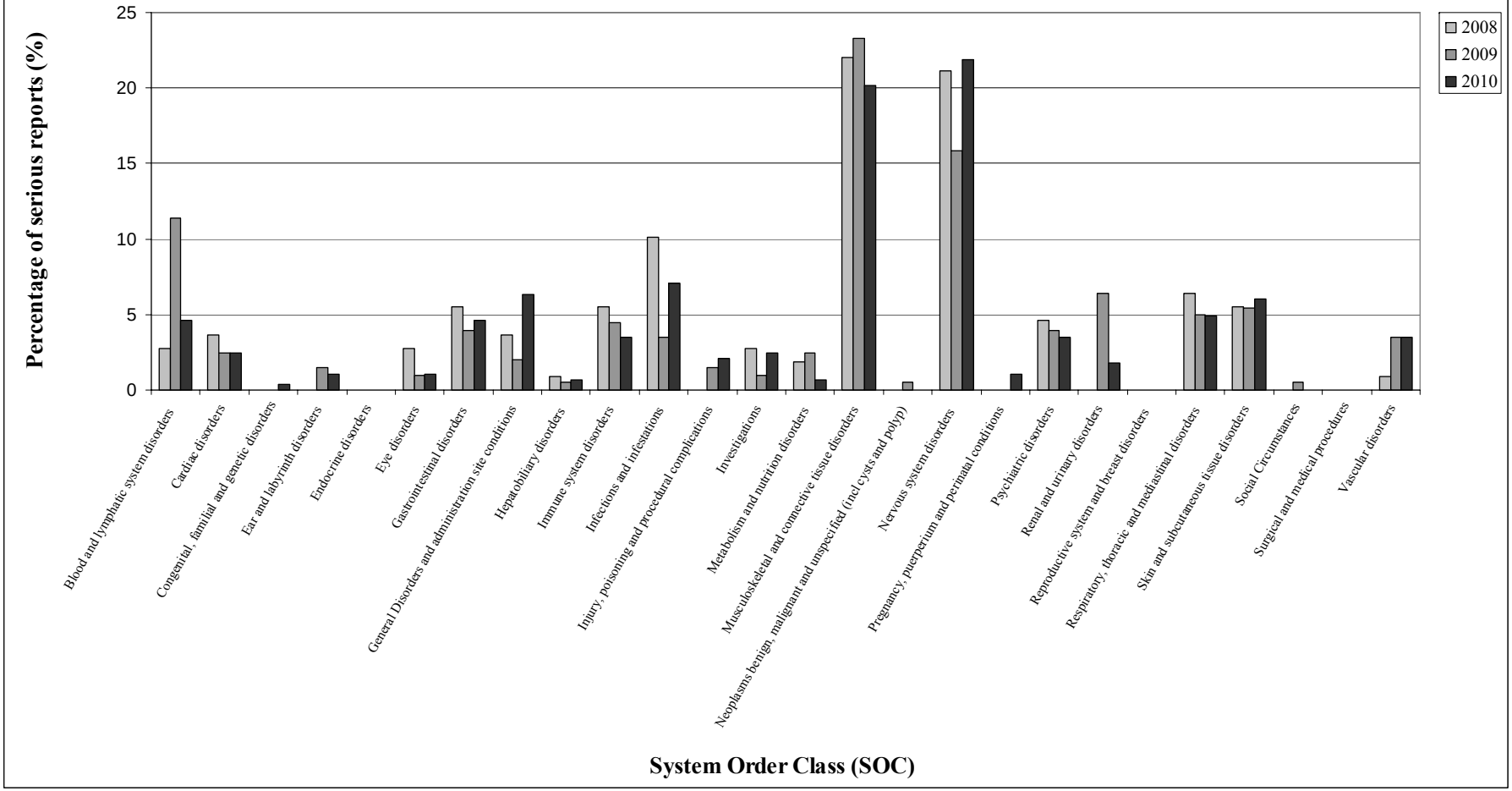
[5]http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Professionalletters/Chiefmedicalofficerletters/DH_127048

There were five suspected ADRs with a fatal outcome in 2010. There were three cases of 'Sudden Death', one case of 'Death' and one case of 'Myocardial Infarction'. A causal association with the influenza vaccines has not been established for any of these cases – the vaccine is largely given to those at high background risk of such events regardless of vaccination.

Please refer to section 2.2 for information regarding CSL influenza vaccines and an association with febrile convulsions.

Conclusion: No significant new safety issues have been identified during 2010. Prior to the 2010/11 influenza season, one influenza vaccine, manufactured by CSL and marketed by Pfizer in the UK (Enzira/CSL vaccine), was found to be associated with an increased risk of febrile convulsions in children. The licence was therefore restricted to use in those aged 5 years and over before it was used in the UK. No other seasonal influenza vaccines have been associated with this risk. This is discussed further below.

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



1.2.3. Pneumococcal polysaccharide vaccine (PPV)

The total number of suspected ADRs reported in association with pneumococcal polysaccharide vaccine for the last 3 years is shown below (table 11).

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

	2008	2009	2010
Total number of reports	86 (24)	40 (12)	66 (33)
Total number of reactions	241 (44)	109 (16)	197 (50)
Total fatal	3	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 2010 were not available at the time of writing this report and as such, ERRs have not been calculated.

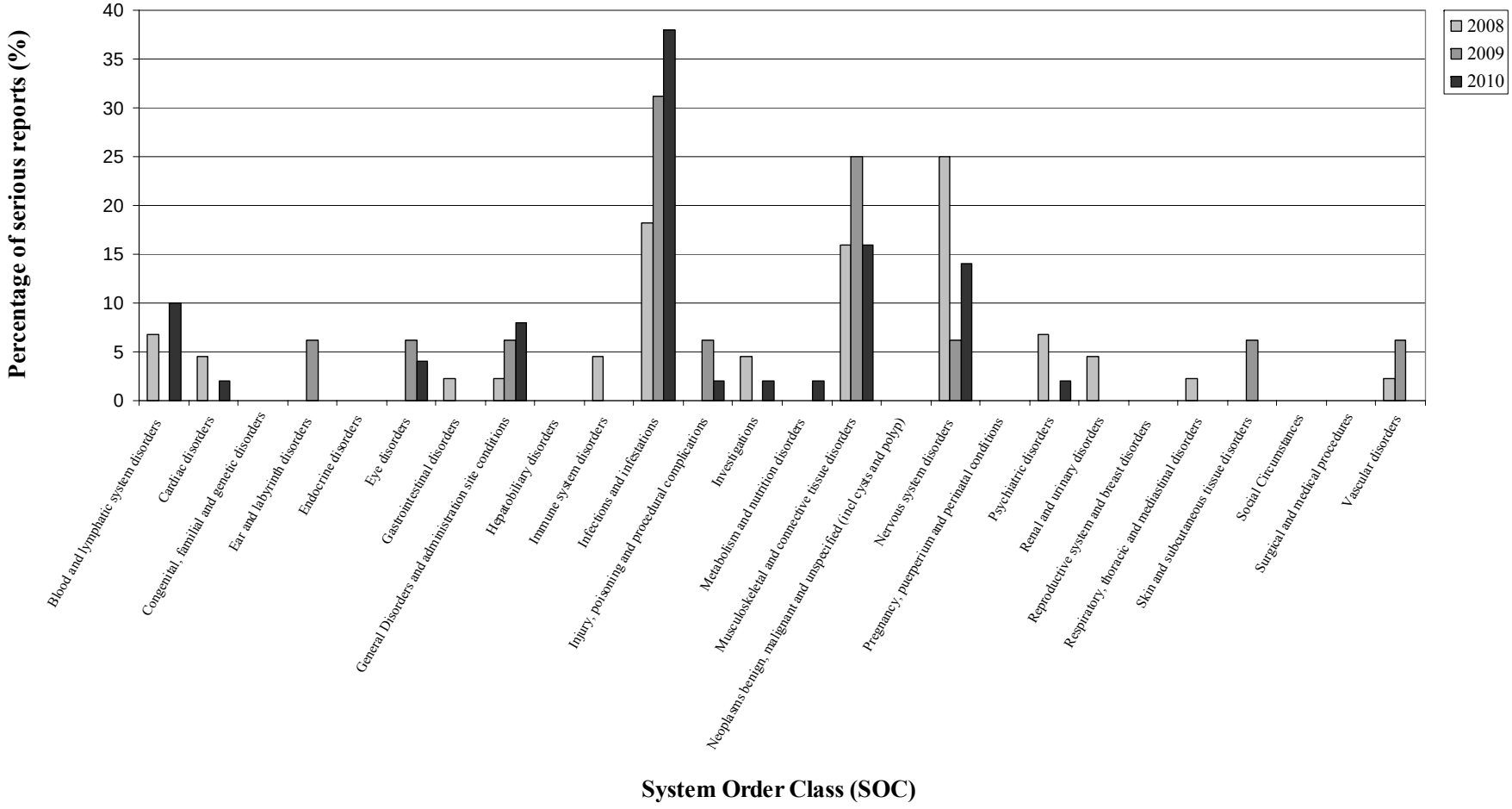
Figure 12 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. The majority of serious reactions occurred within the 'Infections and Infestations' SOC. The most reported serious reaction in this SOC is 'Cellulitis' (13 cases of 'Cellulitis' and 3 reports of 'Injection Site Cellulitis'), which is a recognised reaction as a local reaction.

The SPC with the second highest proportion of serious reactions was the 'Musculoskeletal and Connective Tissue Disorders' SOC. The most reported serious reaction in this SOC is 'Myalgia' (4 cases), which is also a recognised reaction to vaccination.

There was one fatal report associated with pneumococcal polysaccharide vaccine in 2010, of 'Pneumonia Streptococcal'. However, it was unconfirmed whether the patient actually received the vaccination in the first instance.

Conclusion: No significant new safety issues have been identified during 2010.

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



1.2.4. BCG vaccine

The aim of the UK BCG immunisation programme is to immunise those at increased risk of developing severe disease and/or of exposure to TB infection

The total number of suspected ADRs reported in association with BCG vaccine for the last 3 years is shown below (table 12). Exposure figures are based on data from England[1].

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

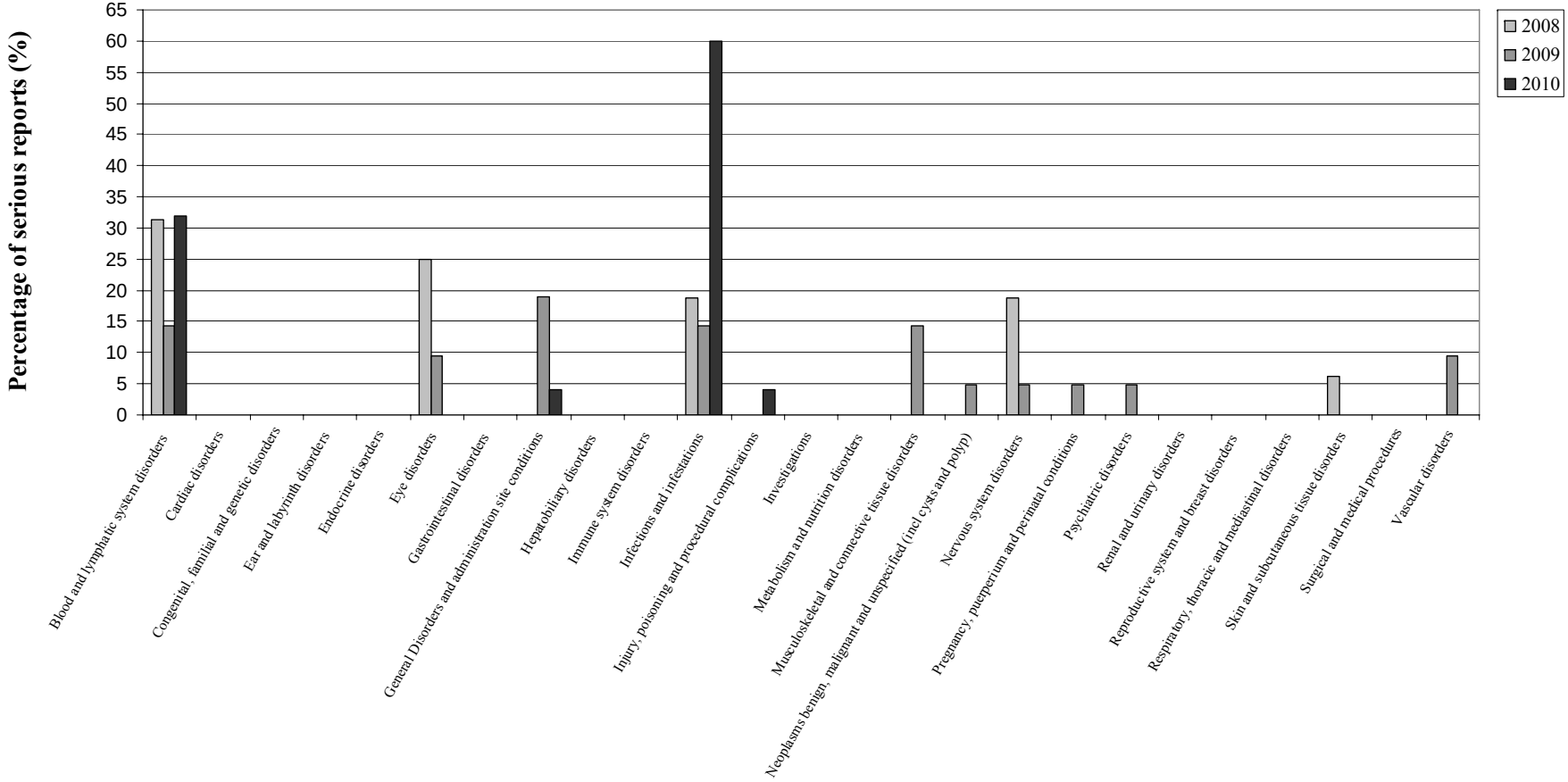
	2008	2009	2010
Total number of reports	32 (13)	25 (14)	40 (24)
Total number of reactions	49 (16)	44 (21)	76 (25)
Total fatal	0	2	1
Exposure (doses)	217,294	239,186	223,167
ERR per 100,000 doses	14.7 (5.9)	10.5 (5.8)	17.9 (10.7)

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

Figure 13 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 'Infections and Infestations' SOC and the 'Blood and Lymphatic System Disorders' SOC. The majority of the reactions reported in these SOCs were tuberculosis (7 'Pulmonary Tuberculosis', 3 'Lymph Node Tuberculosis', 2 'Bovine Tuberculosis' and 2 'Tuberculosis'), and 'Lymphadenitis' and 'Lymphadenopathy' (6 cases and 2 cases respectively). Lymphadenopathy and disseminated tuberculosis infections are both recognised reactions for BCG vaccine.

Conclusion: No significant new safety issues have been identified during 2010.

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



1.2.5. Varivax▼, Varilrix and Zostavax (Varicella Zoster virus) vaccines

Since 2003, the UK recommendation includes vaccinating non-immune healthcare workers who themselves will derive benefit as they will be protected from contact with infectious patients. Varicella vaccine is also recommended for healthy susceptible close household contacts of immunocompromised patients.

No reports concerning Zostavax vaccine (shingles vaccine) were received between 2008 and 2010.

Table 13: Total number of Varicella Zoster vaccine reports (serious reports in brackets)

	2008	2009	2010
Total number of reports	19 (12)	13 (6)	11 (7)
Total number of reactions	49 (24)	38 (10)	32 (12)
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.

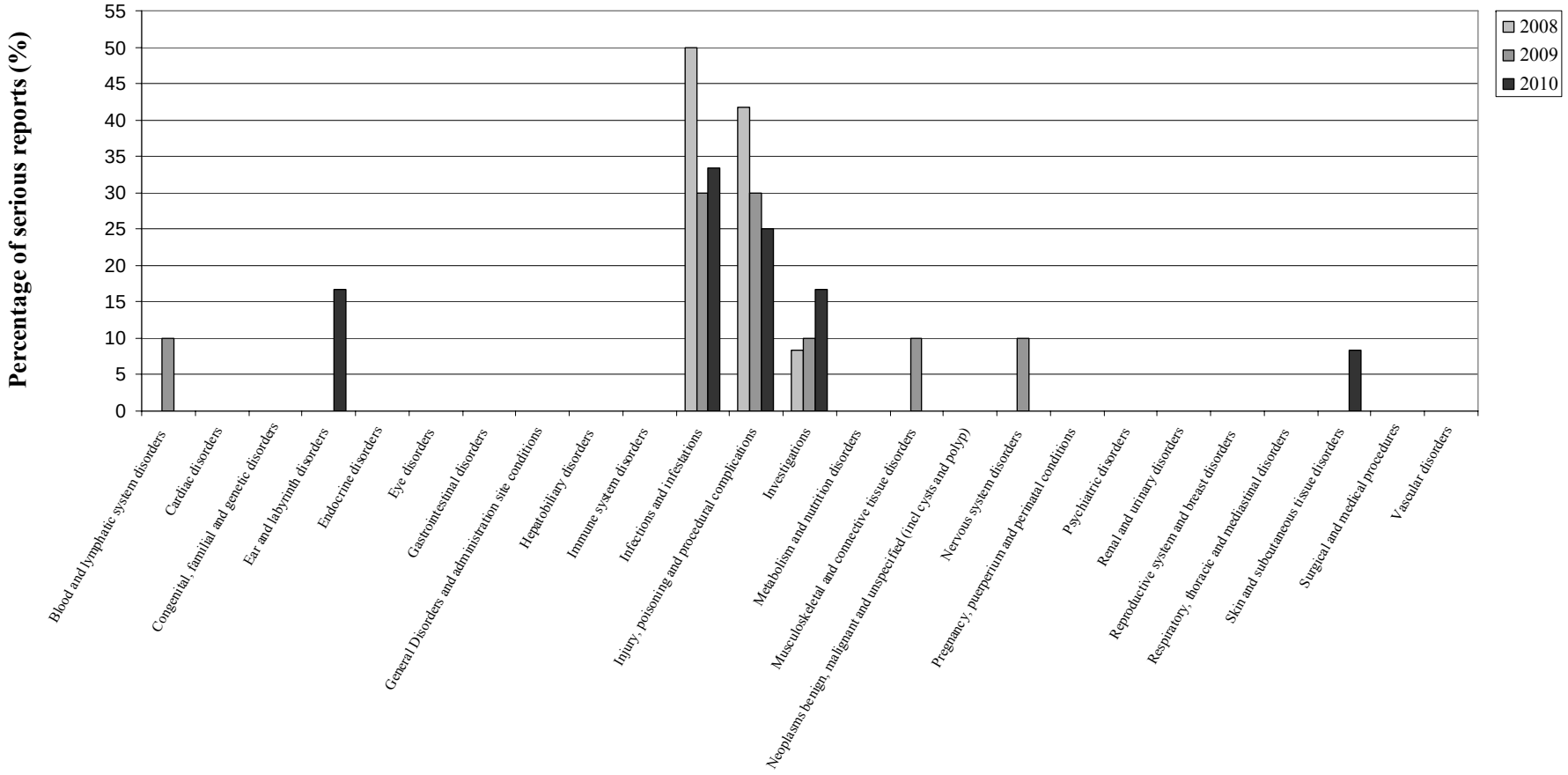
The usage data for the vaccines was not available at the time of writing this report and as such, ERRs have not been calculated.

Figure 14 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 'Infections and infestations' SOC and the 'Injury, poisoning and procedural complications' SOC. These were mainly 'Varicella' (4 cases) and 'Vaccination Failure' (3 cases). The reactions 'Deafness Neurosensory' and 'Deafness Unilateral' are both derived from a single report. Figure 12 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 Varilrix were updated in 2008 to include a two-dose schedule in order to provide long-term protection.

Conclusion: No significant new safety issues have been identified during 2010.

Figure 14: 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 2010 AND TO DATE

2.1 Pandemrix and Narcolepsy

In August 2010, several reports of narcolepsy in Sweden and Finland following use of Pandemrix swine flu vaccine came to light. At the time, there had been no reports of narcolepsy in the UK or other countries following the vaccine. This safety signal prompted an EU–wide safety review. As EU 'Rapporteur' for Pandemrix, the MHRA led on the safety review.

This regulatory review concluded in July 2011, with a recommendation that Pandemrix vaccine may only be used in persons aged under 20 years if seasonal trivalent vaccine is not available and if there is a particular need to immunise against H1N1. No restrictions on use in adults were imposed, and the overall balance of risks and benefits remains favourable.

Underpinning the risk assessment were three epidemiological studies carried out in Sweden and Finland, where most reports of narcolepsy following the vaccine have occurred. Pandemrix was the only vaccine used in these countries. The studies suggested a six to thirteen-fold increased risk of narcolepsy amongst vaccinated children, with a vaccine-attributable risk of three to seven extra cases of narcolepsy per 100,000 doses. No increased risk in those aged above 19 years has been identified. Throughout the EU review, questions have been raised around whether changes in diagnostic practice, bias or confounding may have explained the results. However, the review concluded that any such factors could not fully account for the observed level of risk. It was also concluded that this association was likely due to some sort of temporal/geographic interaction between vaccine and environmental factors during the peak of the pandemic. Any such co-factors remain unknown, but it is speculated that concurrent respiratory infections, including H1N1 itself, may have played a role. Genetic predisposition may also have been an influence. These factors remain unknown, and further studies are ongoing to explore this.

Although several other EU countries, including the UK, have now reported isolated cases of narcolepsy after the vaccine following the media interest from the Nordic area, this risk has not been confirmed in other countries so far. Studies are being carried out to assess if this may be limited to Sweden and Finland.

This safety signal is so far not apparent for other types of influenza vaccine, and the safety review was limited to Pandemrix vaccine. Vaccines used outside of Europe, including a similar GSK vaccine used in Canada and unadjuvanted vaccines used elsewhere have so far not been associated with this signal

The annual seasonal, trivalent flu vaccines have not been associated with the development of narcolepsy, and there are no new safety concerns associated with these vaccines. Seasonal, trivalent flu vaccines remain recommended for protection against seasonal influenza.

More information on the EU review of narcolepsy can be found at
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/07/n

ews_detail_001312.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1.

2.2 CSL/Enzira seasonal flu vaccine and febrile convulsions

In Australia in April 2010, an excess risk of febrile convulsions was found to be associated with a brand of flu vaccine called Fluvax, manufactured by CSL. A similar CSL vaccine was on the UK market branded as Enzira or as CSL Biotherapies' generic influenza vaccine in the 2010/11 influenza vaccine campaign. Therefore, prior to use in the UK during 2010/11, the licence for Enzira/CSL Biotherapies' generic influenza vaccine was restricted for use only in those aged 5 years and over.

Although there was no suggestion that other influenza vaccines supplied in the UK may be associated with a similar risk, as a precaution the MHRA implemented enhanced passive surveillance to closely monitor the safety of all influenza vaccines used in the UK during the 2010/11 campaign. This analysis found no indication of an excess risk of febrile convulsions in children following use of other (non-CSL/Pfizer) seasonal flu vaccines in the UK.

For further information regarding this issue please refer to the MHRA's Public Assessment Report on seasonal flu vaccines and febrile seizures, available at http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON103043.

2.3 Post Pandemic Safety Review

In July 2010, MHRA performed a post-pandemic review of all suspected ADRs reported in the UK in association with the swine flu vaccines Pandemrix and Celvapan during the pandemic period. Up to 18 June 2010, more than 6 million doses of Pandemrix, and more than 36 000 doses of Celvapan, were given across the UK. Out of these, there were 3,400 reports of suspected ADRs with Pandemrix, and 43 reports of suspected ADRs with Celvapan.

As with many vaccines, the vast majority of the reported reactions related to injection-site reactions and the signs and symptoms of a mild 'flu-like' illness. Despite substantial usage over a very short period, no significant safety issues were identified for either vaccine. Data on reports of Guillain Barre Syndrome (GBS) in particular were examined, as this condition has been reported in the past as a suspected rare side effect of swine flu influenza vaccines used in the United States in 1976. However, GBS can also occur following infections (particularly flu-like illness), and can develop spontaneously without any obvious cause. There is currently no confirmed evidence to indicate that either the Pandemrix or Celvapan vaccine is associated with an increased risk of GBS. The safety profile of both vaccines during the pandemic period was as expected, and broadly similar to the established profiles for seasonal influenza vaccines.

The UK safety profile of the vaccines was supported by the international experience. It was estimated that at least 30 million and 566,000 people were vaccinated with Pandemrix and Celvapan, respectively, across Europe during the pandemic (note: the narcolepsy safety signal in Sweden and Finland came to light after this UK safety review – at the time, there were no UK reports of narcolepsy following Pandemrix).

The full safety review can be found at www.mhra.gov.uk/swineflu.