Paper provided by MHRA for
Joint Committee on Vaccination and Immunisation
October 2014:

VACCINE-ASSOCIATED SUSPECTED ADVERSE REACTIONS REPORTED VIA THE YELLOW CARD SCHEME DURING 2013/14

September 2014

Medicines and Healthcare Products Regulatory Agency

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Introduction

This paper was prepared by the Medicines and Healthcare products Regulatory Agency (MHRA) for the October 2014 Meeting of the Joint Committee of Vaccination and Immunisation (JCVI).

This paper provides an update on UK suspected adverse reactions (ADRs) associated with routine and/or commonly used vaccines reported to the MHRA via the Yellow Card Scheme during the time period of 1st July 2013 to 30th June 2014.

It should be noted that a report of a suspected ADR to the MHRA 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 (http://www.medicines.org.uk/emc/).

Furthermore, due to variable levels of reporting and as the precise number of individuals immunised is not included in this report, 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 COVER uptake data extrapolated to the relevant UK birth cohort. Exposure for non-routine vaccines has not been estimated in this report. As the reporting rates are broad estimates which do not take into account exposure outside of the routine schedule, and are not age-adjusted, no firm conclusions can be drawn on relative ADR reporting rates over time.

Yellow Card reports may contain more than one ADR. Seriousness is determined by regulatory criteria based on the medical condition (MedDRA Dictionary serious)[1] and whether the reporter considers the report to be serious (CIOMs seriousness criteria[2]). Yellow Card data covers the whole of the UK. CIOMs is an additional criteria applied in this report and, therefore, the proportion of serious ADRs will differ compared to previous reports.

Prepared: September 2014

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

[1] MedDRA - the Medical Dictionary for Regulatory Activities - is a standardised, medically validated adverse event terminology system used within the international medicines regulatory environment.

[2] CIOMs- Council for International Organizations of Medical Sciences- defined as 6 possible categories which are documented on the Yellow Card. The criteria are: (1) patient died due to reaction (2) life threatening (3) resulted in hospitalisation or prolonged inpatient hospitalisation (4) congenital abnormality and (5) involved persistent or significant disability or incapacity or (6) if the reaction was deemed medically significant

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.

The total number of suspected ADRs reported in association with Menitorix over the last 3.5 years is shown below (table 1). 2013/2014 exposure is based on the assumption of 92% uptake (one dose) for an annual birth cohort of up to 800,000[3]. Note: the 2012/13 extract period was 18 months, whereas the 2011 and 2013/14 period were both 12 months, hence the difference between denominators.

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

	2011	2012/13	2013/14
Total number of reports	18 (15)	35 (25)	37 (20)
Total number of reactions	40 (31)	123 (90)	95 (60)
Total fatal	1	0	1
Exposure	736,000	1,116,000	736,000
ERR per 100,000 doses	2.4 (2.0)	3.1 (2.2)	5.0 (2.7)

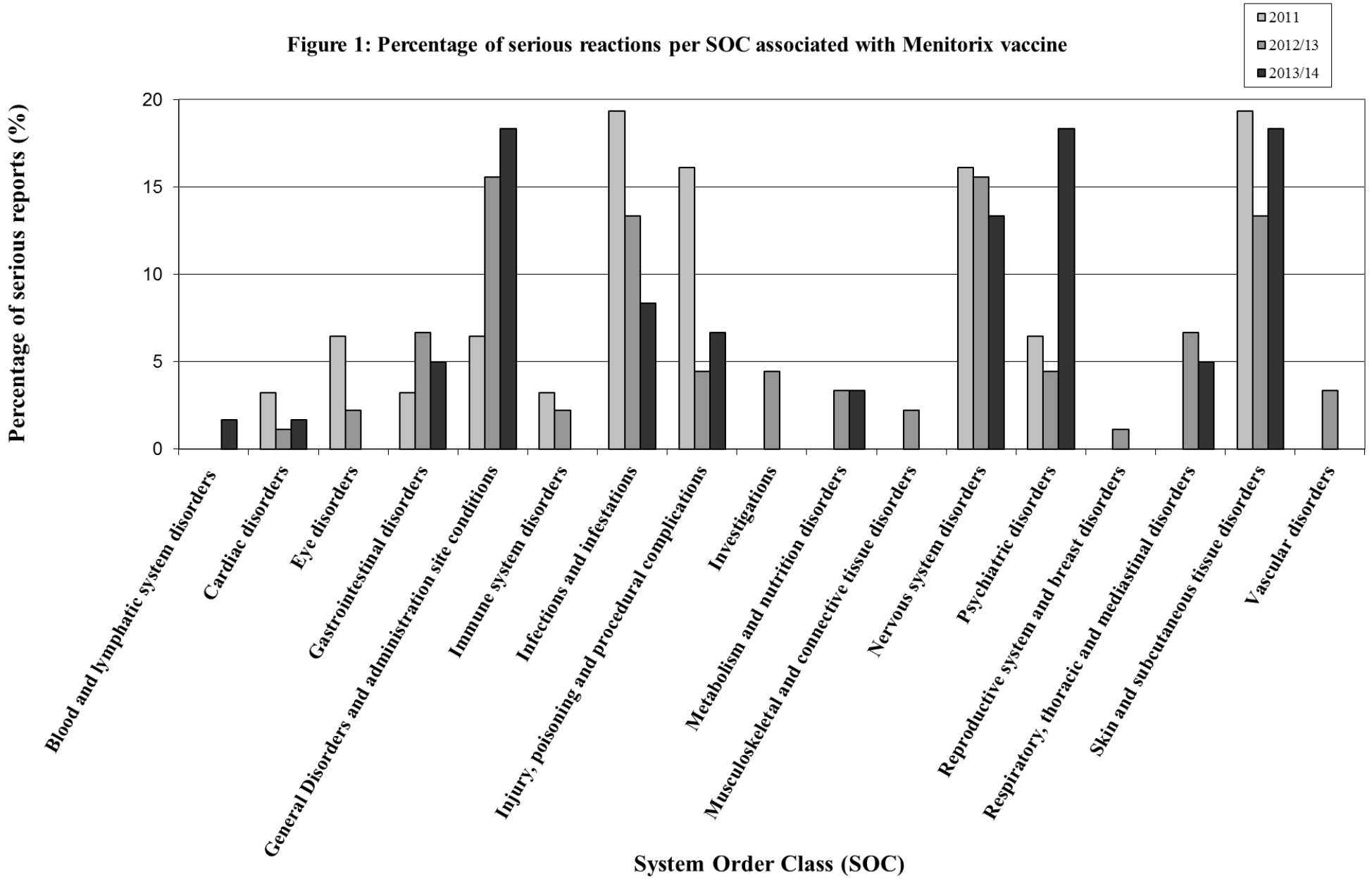
ERR = Estimated Reporting Rate

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 and a half years. Reporting rates have remained consistently very low. As number of reports is low, any relative percentage changes should be interpreted with caution.

The 'General Disorders and administration site conditions', 'Psychiatric disorders' and 'Skin and subcutaneous tissue disorders' SOC each accounted for 18% of all serious reactions. The reactions reported are well recognised e.g. irritability ('Psychiatric' SOC); injection site reactions and pyrexia ('General Disorders and administration site conditions' SOC); and rash and facial swelling ('Skin and subcutaneous tissue disorders' SOC). Other reports were spread across 8 SOCs, and concerned either known rare side effects of primary immunisation or events likely coincidental with vaccination. There was one suspected ADR ('Sudden death') with a fatal outcome in 2013/14. A causal association with vaccination has not been established for this case. One of the serious reports related to consequences of meningococcal infection which was a possible vaccine failure. As with all vaccines, meningitis C and *Haemophilus* type B vaccination may not be 100% effective.

Conclusion: No significant new safety issues were identified during 2013/14

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



1.1.2. Prevenar 13 (pneumococcal conjugate vaccine)

In April 2010, Prevenar vaccine (PCV7) was replaced by Prevenar 13 (PCV13), which contains antigens against 13 strains, to broaden protection against pneumococcal disease. Prevenar is offered routinely at 2 and 4 months of age, and as a booster around/shortly after the first birthday.

2013/14 exposure is based on the assumption of combined 93% uptake for two primary doses and one booster dose for an annual birth cohort of up to 800,000. Note: the 2012/13 extract period was 18 months, whereas the 2011 and 2013/14 period were both 12 months, hence the difference between denominators.

Table 2: Total number of Prevenar 13 reports (serious reports in brackets)

	2011	2012/13	2013/14
Total number of reports	184 (151)	194 (148)	141 (104)
Total number of reactions	517 (426)	615 (509)	455 (358)
Total fatal	5	4	4
Exposure	1,463,200	3.348,000	2,232,000
ERR per 100,000 doses	12.6 (10.3)	5.8 (4.42)	6.3 (4.7)

ERR = Estimated Reporting Rate

The 104 serious reports were spread across 22 SOCs, with a large amount falling into the 'Infections and infestations' SOC and concerned mainly isolated events which were either known rare side effects of primary immunisation or likely to be events coincidental with vaccination. There were 39 cases of pneumococcal infection (one fatal outcome), 5 of meningitis pneumococcal, 2 of pneumococcal sepsis and 1 of pneumonia pneumococcal. As with all vaccines, pneumococcal conjugate vaccination may not be 100% successful and isolated cases of failure following primary vaccination are not unexpected.

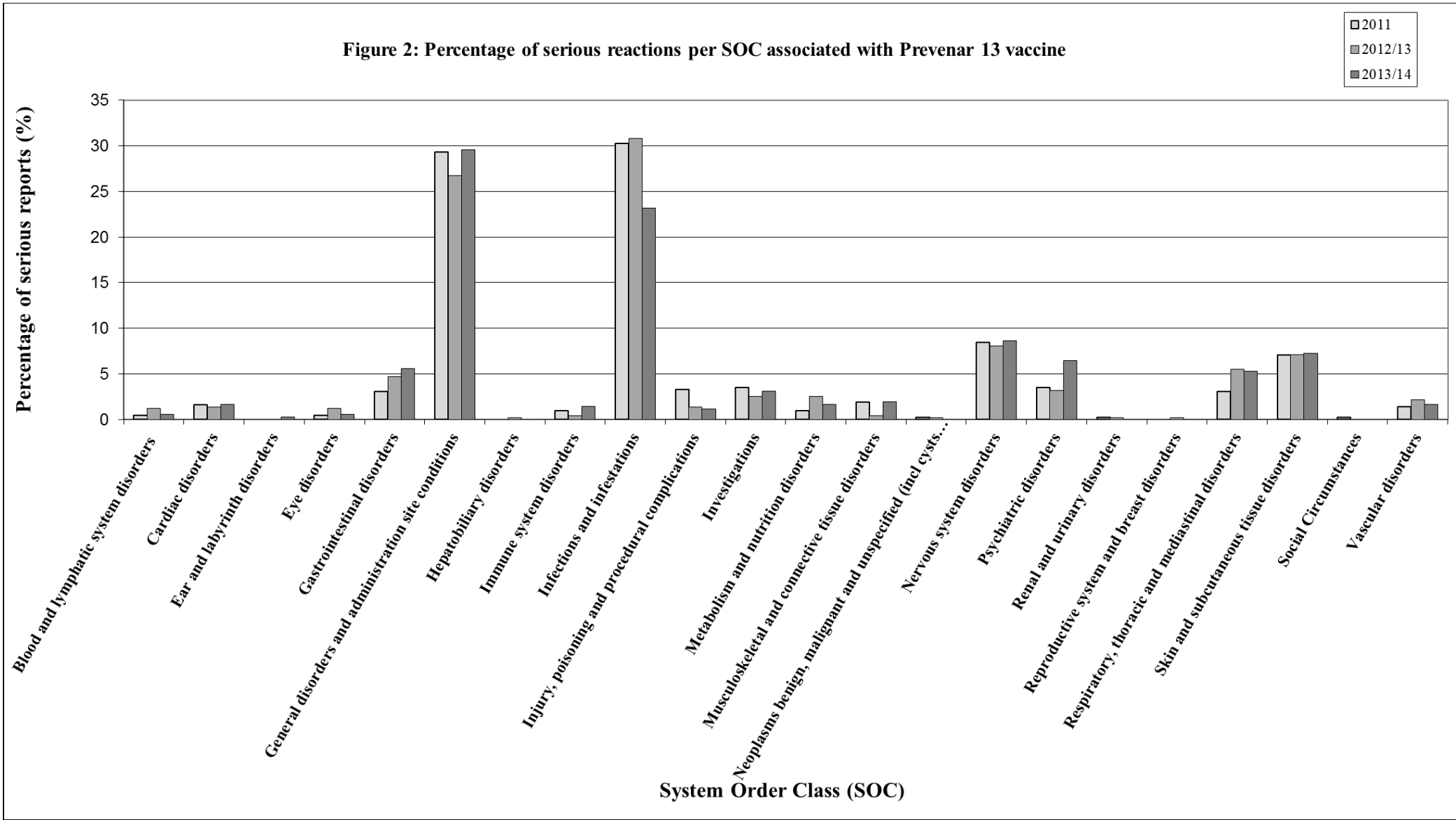
Three other fatal reports were received, with reactions of death unexplained, sudden death unexplained and cardiac arrest. A causal association with vaccination has not been established for any of these cases.

The majority of serious events fall into the 'General disorders and administration site conditions' SOC and concerned events such as injection site reactions and cases of 'drug ineffective' terms, as isolated case of vaccine failure may occur.

Figure 2 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three and a half years.

Conclusion: No significant new safety issues were identified during 2013/14.

Figure 2: Percentage of serious reactions per SOC associated with Prevenar 13 vaccine



1. 1.3. Pediacel and Infanrix IPV Hib (DTPa/IPV/Hib)

DTPa/IPV/Hib vaccine is offered routinely at 2, 3 and 4 months of age.

The total number of suspected ADRs reported in association with DTPa/IPV/Hib for the last 3 and half years is shown below (table 3). 2013/14 exposure is based on the assumption of 95% uptake (3 doses) for an annual birth cohort of up to 800,000. Note: the 2012/13 extract period was 18 months, whereas the 2011 and 2013/14 period were both 12 months, hence the difference between denominators.

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

	2011	2012/13	2013/14
Total number of reports	82 (57)	133 (83)	94 (69)
Total number of reactions	261 (180)	416 (272)	326 (262)
Total fatal	0	0	2
Exposure	2,280,000	3,420,000	2,304,000
ERR per 100,000 doses	3.6 (2.5)	3.8 (2.4)	4.1 (3.0)

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. Reporting rates have remained consistently very low.

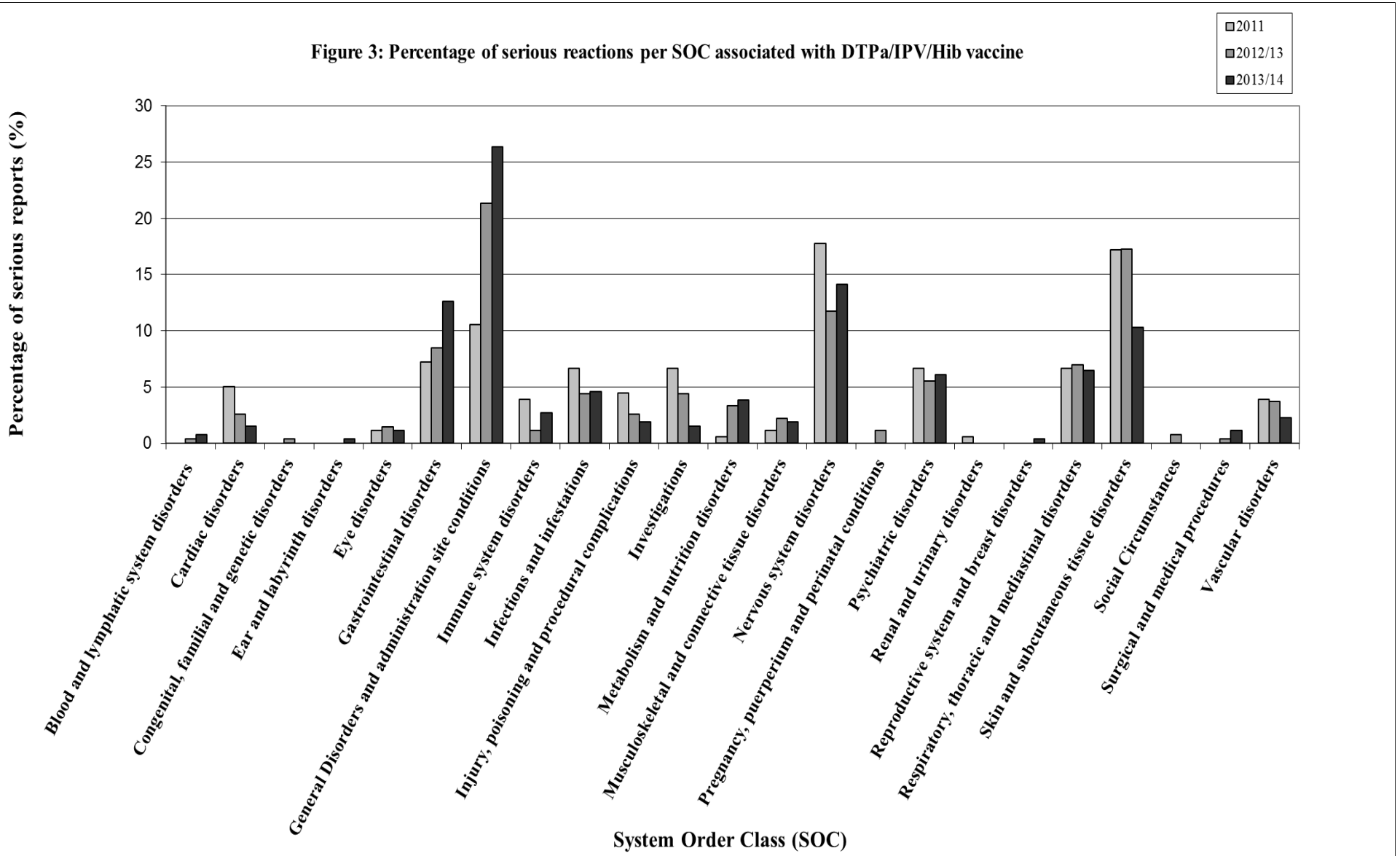
The 69 serious reports were spread over 23 SOCs. The majority of serious reactions were in the General disorders and administration sire conditions including injection site reactions including injection site reactions and pyrexia.

As in previous years, most Nervous System Disorders related to the known rare side effects of convulsions, hypotonic-hyporesponsive episodes, as well as reports of syncope. The slight increase in proportion of gastrointestinal reactions in 2013/14 may be due to reports of diarrhoea and vomiting co-suspect with Rotarix. The remaining serious reports concerned a wide range of isolated events which were either known rare side effects or likely coincidental with vaccination.

There were 2 fatal cases reported in 2013/14, 1 report of “death” and 1 report of “hypoxia”. A causal association with the DTaP IPV Hib vaccine has not been established for either of these cases.

Conclusion: No significant new safety issues were identified during 2013/14.

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 offered at 12-13 months of age, with a second dose from 3 years 4 months. MMR may also be offered at anytime to unimmunised individuals.

The total number of suspected ADRs reported in association with MMR vaccination for the last 3 and a half years is shown below (table 4). 2013/14 exposure is based on the assumption of 92% uptake for 2 doses, for an annual birth cohort of up to 800,000. Note: the exposure estimates are based on only routine childhood use. Data on non-routine use, and use in any catch-up campaigns, are not available to MHRA at the time writing. MMR catch-up initiatives are likely to account for the increase in total number of ADR reports since 2011. Exposure is therefore a underestimate. Note: the 2012/13 extract period was 18 months, whereas the 2011 and 2013/14 period were both 12 months.

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

	2011	2012/13	2013/14
Total number of reports	145 (119)	246 (186)	229 (172)
Total number of reactions	418 (322)	891 (658)	730 (568)
Total fatal	0	0	2
Exposure	1,408,800	2,160,000	1,472,000
ERR per 100,000 doses	10.3 (8.4)	11.4 (8.6)	15.6 (11.7)

ERR = Estimated Reporting Rate

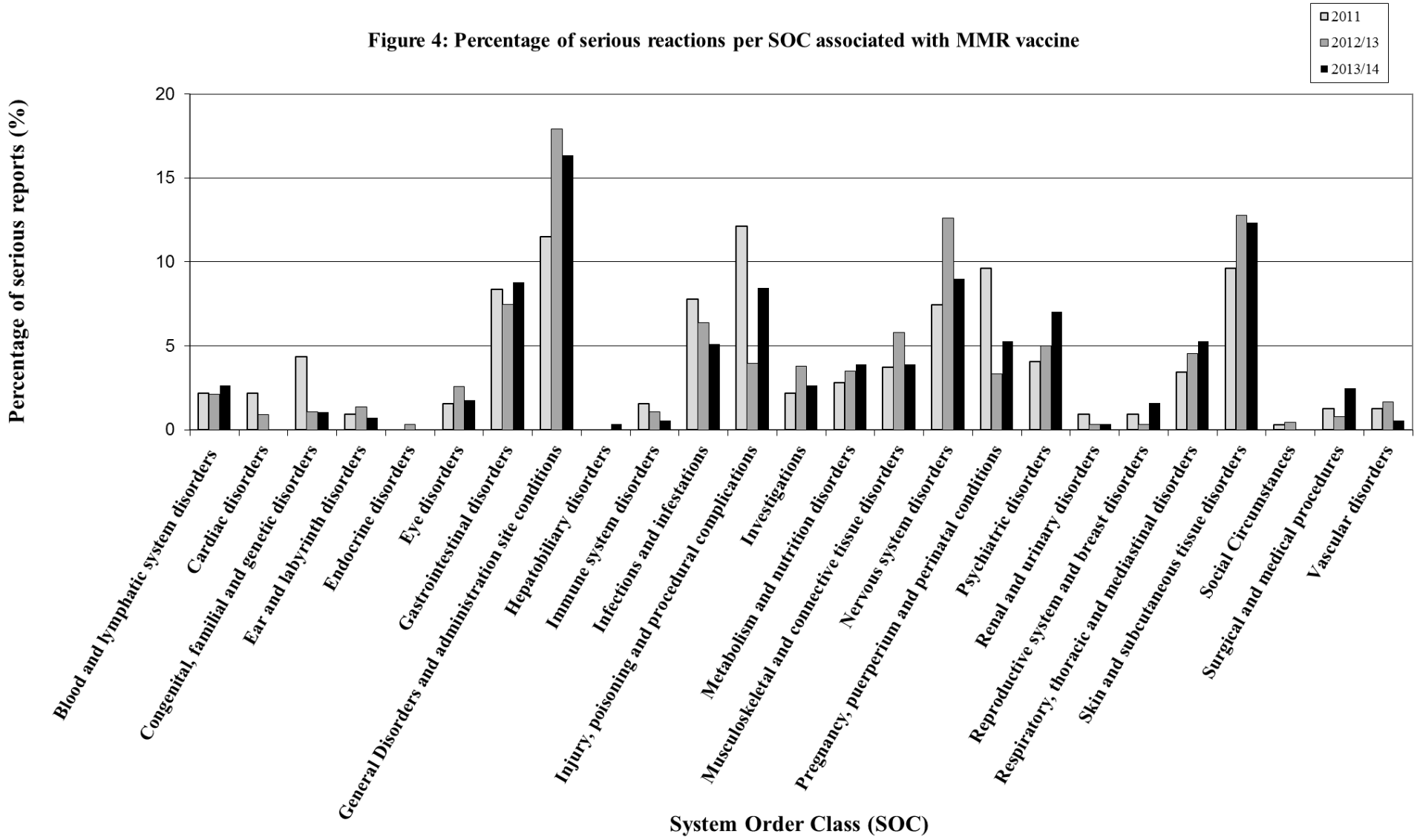
Figure 4 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three and a half years. The 172 serious reports were spread over 22 SOCs.

The majority of serious reactions (16%) fall in to the 'General Disorders and administration site conditions' SOC and include reactions such as pyrexia and injection site reactions including pain, swelling and rash. Most reported 'Musculoskeletal and Connective Tissue Disorder' related to arthralgia or myalgia, which are listed as possible side effects in the SmPC.

There were two suspected ADRs with a fatal outcome in 2013/14: foetal death and sudden death. A causal association with vaccination has not been established for these cases. The serious reports concerned a wide range of isolated events which were either known rare side effects or likely coincidental with vaccination.

Conclusion: No significant new safety issues were identified during 2013/14

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



1.1.5. Meningitis C vaccine

During the period of this report, single component meningococcal group C conjugate vaccine was offered routinely as a single dose at 3 months of age and a booster dose at around 14 years of age (with a MenC/Hib booster at 12-13 months old).

The total number of suspected ADRs reported in association with Meningococcal group C conjugate vaccine for the last 3 and a half years is shown below (table 5). As uptake for the teenage booster dose is not available at the time of writing, and as there was also a catch-up dose for universityentrants during the extract period, a denominator for MenC vaccine cannot be reliably estimated for 2013/14. Therefore, a calculation for ERR is not made. Note: the 2012/13 extract period was 18 months, whereas the 2011 and 2013/14 period were both 12 months.

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

	2011	2012/13	2013/14
Total number of reports	60 (42)	75 (54)	143 (91)
Total number of reactions	207 (156)	211 (161)	517 (298)
Total fatal	2	0	1
Exposure	1,494,400	3,420,000	n/a
ERR per 100,000 doses	1.0 (2.8)	2.2 (1.6)	n/a

ERR = Estimated Reporting Rate

Figure 5 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the past 3 and a half years

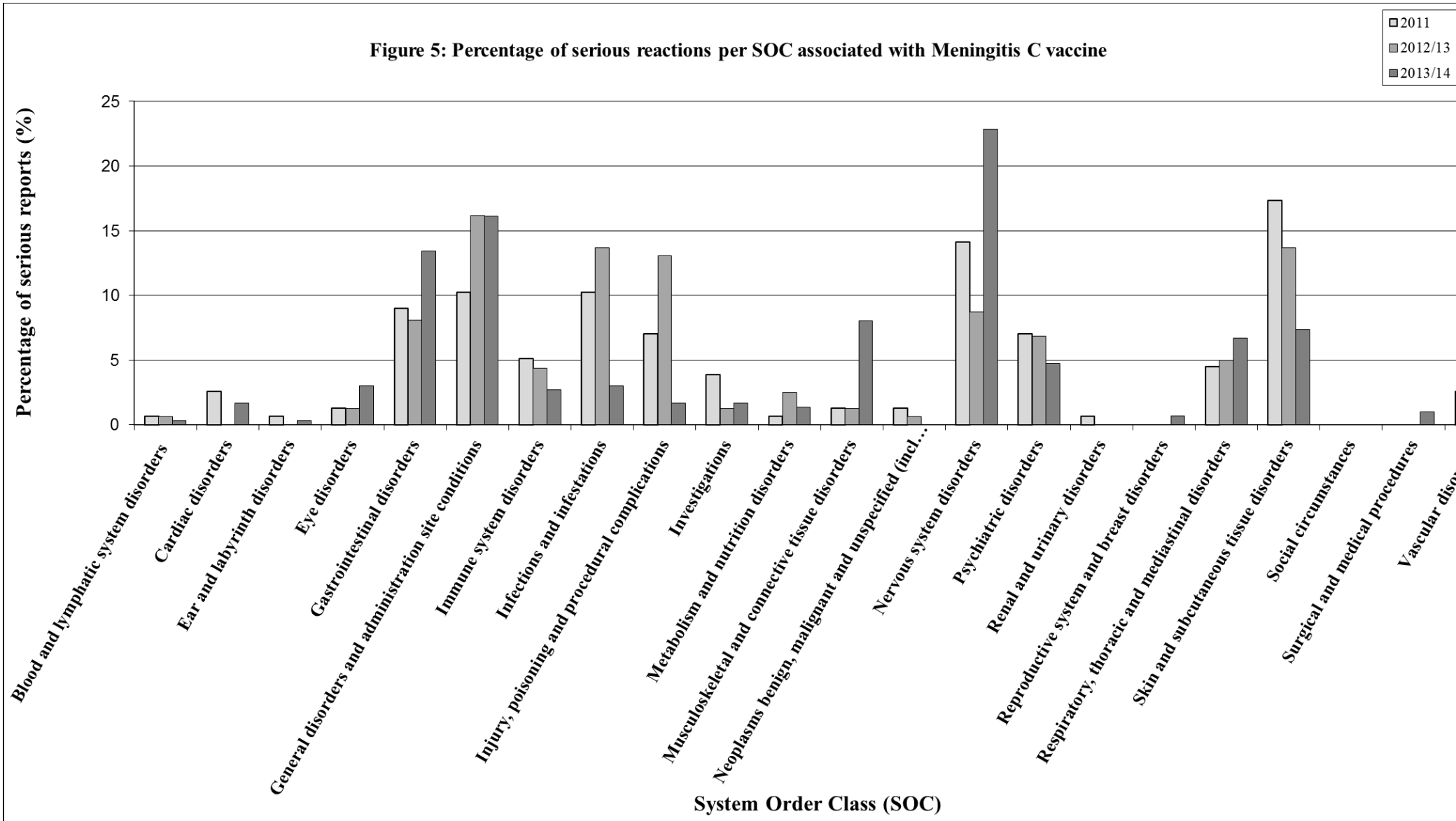
The 91 serious reports were spread over 22 SOCs with the majority of reactions in the 'Nervous systems disorders' SOC. This included 23 reports of syncope, 6 reports of headache and 6 reports of convulsion. The other serious reports concerned a wide range of isolated events which were either known rare side effects or likely coincidental with vaccination. The slight increase in proportion of gastrointestinal reactions in 2013/14 may be due to reports of diarrhoea and vomiting co-suspect with Rotarix.

One fatal report was received, which is the same case as mentioned above for Prevenar 13. A causal association with vaccination has not been established for this case.

Serious events in the 'General disorders and administration site conditions' SOC mainly related to events such as injection site reactions and pyrexia.

Conclusion: No significant new safety issues were identified during 2013/14.

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 at 3 years 4 months of age. A UK-wide immunisation campaign to offer Repevax (and since mid-2014 Boostrix IPV) to all pregnant women between 28-38 weeks pregnant to protect the newborn baby has been in place since October 2012. In July 2014 it was announced the vaccination programme should continue for another 5 years.

The 2013/14 exposure is based on the assumption of 90% uptake (1 dose) for an annual birth cohort of up to 750,000. An additional estimate of 450,000 doses is included (based on an assumed 60% uptake amongst pregnant women). Therefore, the apparent increased reporting rate should be interpreted with caution given that exposure is underestimated. Note: the 2012/13 extract period was 18 months, whereas the 2011 and 2013/14 period were both 12 months.

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

	2011	2012/13	2013/14
Total number of reports	43 (24)	137 (64)	123 (73)
Total number of reactions	135 (56)	384 (178)	377 (224)
Total fatal	0	7	3
Exposure	687,200	1,068,000	1,125,000
ERR per 100,000 doses	6.3 (3.5)	12.8 (5.99)	11 (6.5)

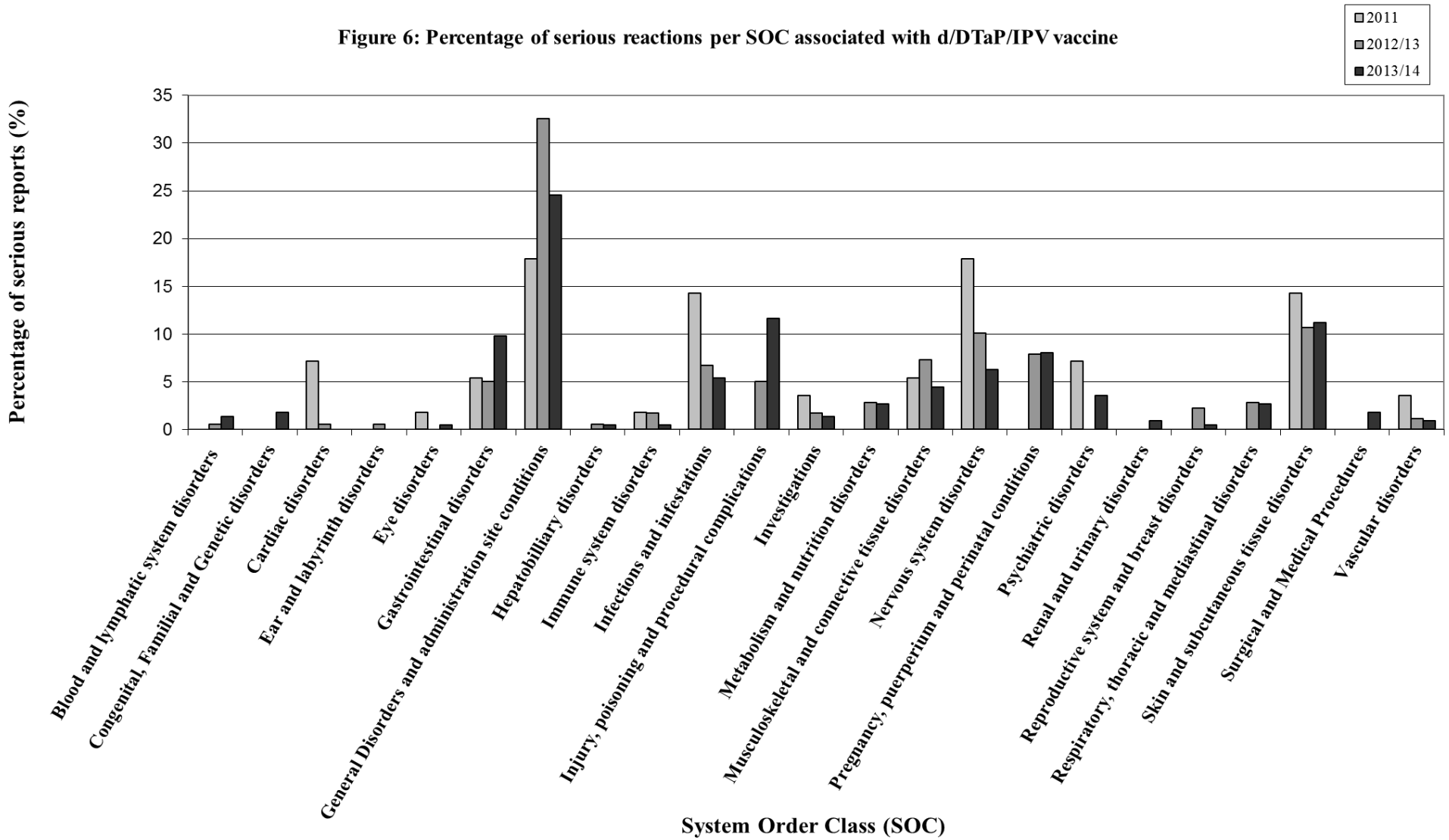
ERR = Estimated Reporting Rate

Figure 6 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last 3 and a half years. Since July 2013, we have received 73 serious reactions which are spread over 23 SOCs and concerned a wide range of isolated events which were either known rare side effects or likely coincidental with vaccination. The most common reactions were in the General disorders and administration site conditions SOC and mainly concerned injection site reaction.

Three suspected ADRs with a fatal outcome were reported in 2013/14. All three reports were associated with the Pregnancy, puerperium and perinatal conditions SOC (2 'Still birth' and 1 'foetal death'). Last year the MHRA undertook a large epidemiological study using the Clinical Practice Research Datalink (CPRD), involving around 18,000 pregnant women, which found no evidence to suggest that Repevax was causally-associated with any adverse pregnancy outcomes, including still birth. These reported fatal events were therefore likely coincidental with vaccination. The study was recently published in the BMJ http://www.bmj.com/content/349/bmj.g4219.

Conclusion: No significant new safety issues have been identified during 2013/14.

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 14 years, 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 and a half years is shown below (table 7).

An estimate of exposure is not given in this paper due to likely widespread use in a wide range of age groups outside of the routine childhood programme. Note: the 2012/13 extract period was 18 months, whereas the 2011 and 2013/14 period were both 12 months.

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

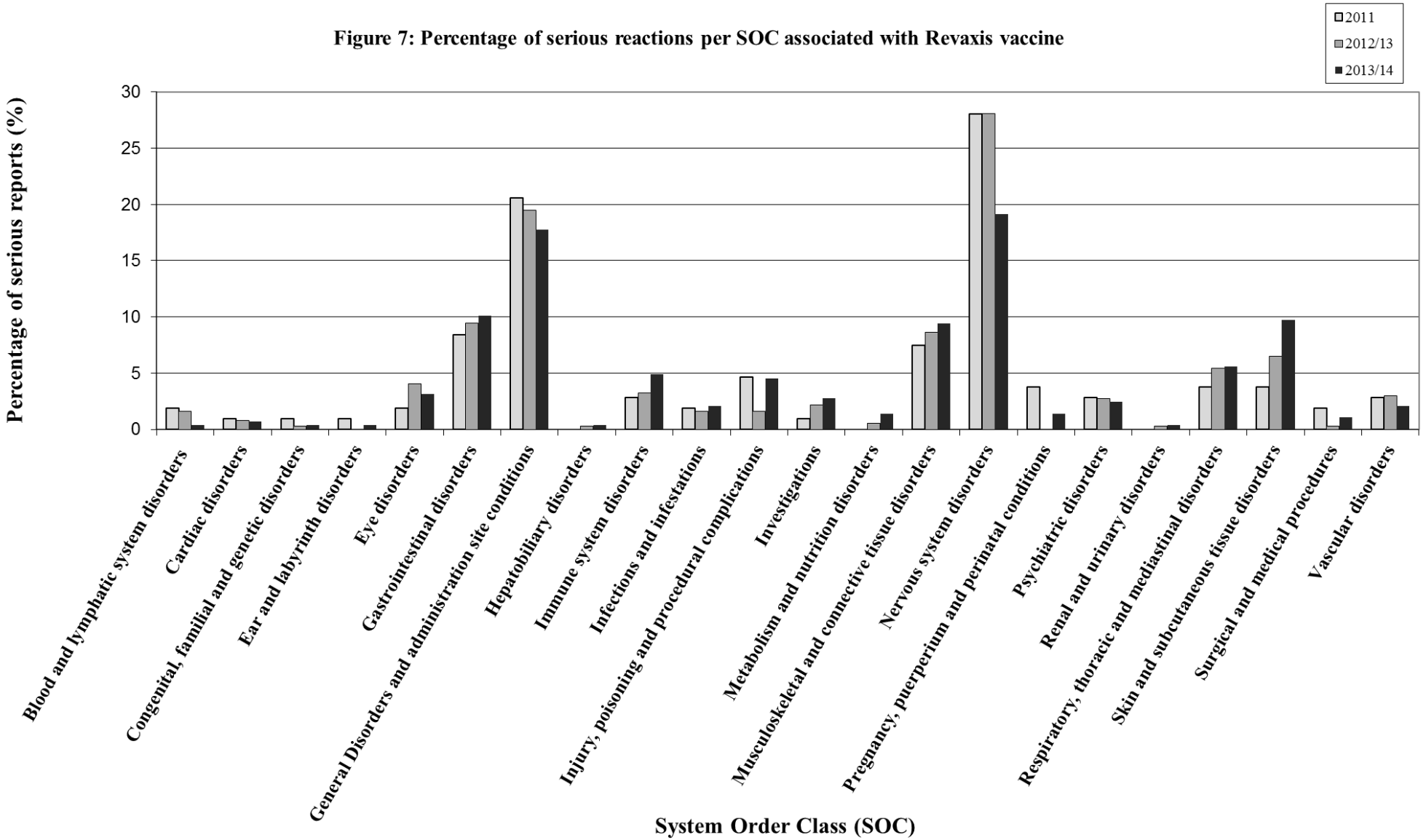
	2011	2012/13	2013/14
Total number of reports	98 (49)	154 (105)	117 (84)
Total number of reactions	277 (107)	622 (370)	445 (287)
Total fatal	0	0	0
Exposure	N/A	N/A	N/A
ERR per 100,000 doses	N/A	N/A	N/A

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

The serious reports were spread over 22 SOCs. The majority of serious reactions (19%) are in the 'Nervous System Disorders' SOC, the most common of which was syncope which is listed as a possible adverse event in the Revaxis SmPC. The 'General Disorders and administration site conditions' SOC accounts for 18% of serious reactions. Reactions reported in this category include pyrexia, and injection site reactions.

Conclusion: No significant new safety issues have been identified during 2013/14.

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



1.1.8. Human Papillomavirus (HPV) vaccines (Cervarix and Gardasil)

In September 2008 Cervarix, which protects against HPV types 16 and 18, was introduced in a new routine HPV immunisation programme for 12 to 13 year-old adolescent girls. This also included an initial catch-up campaign for older teenagers. From September 2012 Gardasil, with HPV types 6, 11, 16 and 18, replaced Cervarix within the national immunisation programme.

The total number of suspected ADRs reported in association with human papillomavirus vaccine for the last 3 and a half years is shown below (table 8). Note: the 2012/13 extract period was 18 months, whereas the 2011 and 2013/14 period were both 12 months. Usage for 2012/13 and 2013/14 is estimated on an assumption of 80% uptake for all three doses from an annual female birth cohort (around the year 2000) of ~330,000.

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

	2011	2012/13	2013/14
Total number of reports	1080 (301)	1090 (360)	549 (227)
Total number of reactions	2434 (867)	2902 (1310)	1566 (855)
Total fatal	0	1	0
Exposure (doses)	790,000	1,185,000	790,000
ERR per 100,000 doses	n/a	92 (30)	70 (28)

The 227 serious reports were spread over 26 SOCs as can be seen in Figure 8. The overall reporting profile has remained broadly consistent.

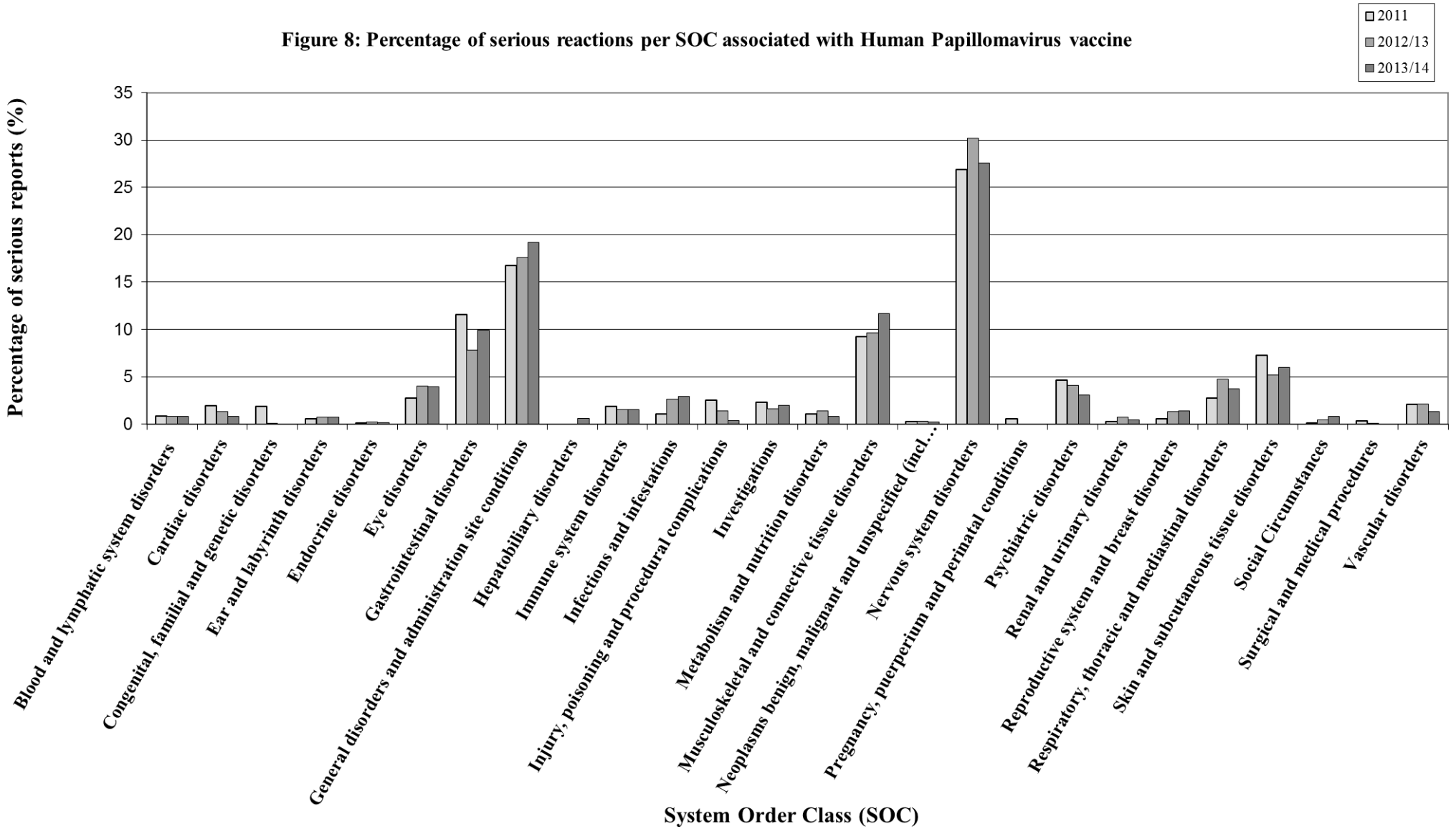
The majority of reactions per SOC are 'Nervous system disorders' which included mainly67 cases of syncope, 35 cases of headache and 29 cases of dizziness. Reactions in the 'General disorders and administration site conditions' SOC and included mainly fatigue, pyrexia and injection site reactions.

The MHRA recently completed an epidemiology study, using the Clinical Practice Research Datalink (CPRD), which found no evidence to suggest that HPV vaccine may be a cause of chronic fatigue syndrome (CFS).. The results of this study have been published in a peer-reviewed scientific journal (*Vaccine* 2013 Aug 31 [Epub ahead of print]) [http://www.sciencedirect.com/science/article/pii/S0264410X13011158].

Further information regarding HPV vaccine, including MHRA's public safety assessment reports, can be found on the MHRA website at www.mhra.gov.uk/HPVvaccine.

Conclusion: No significant new safety issues have been identified during 2013/14

Figure 8: 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). Note: the 2012/13 extract period was 18 months, whereas the 2011 and 2013/14 period were both 12 months.

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

	2010	2011	2012/13
Total number of reports	122 (62)	129 (90)	88 (58)
Total number of reactions	411 (233)	473 (332)	356 (242)
Total fatal	0	0	0
Exposure (doses)	n/a	n/a	n/a
ERR per 100,000 doses	n/a	n/a	n/a

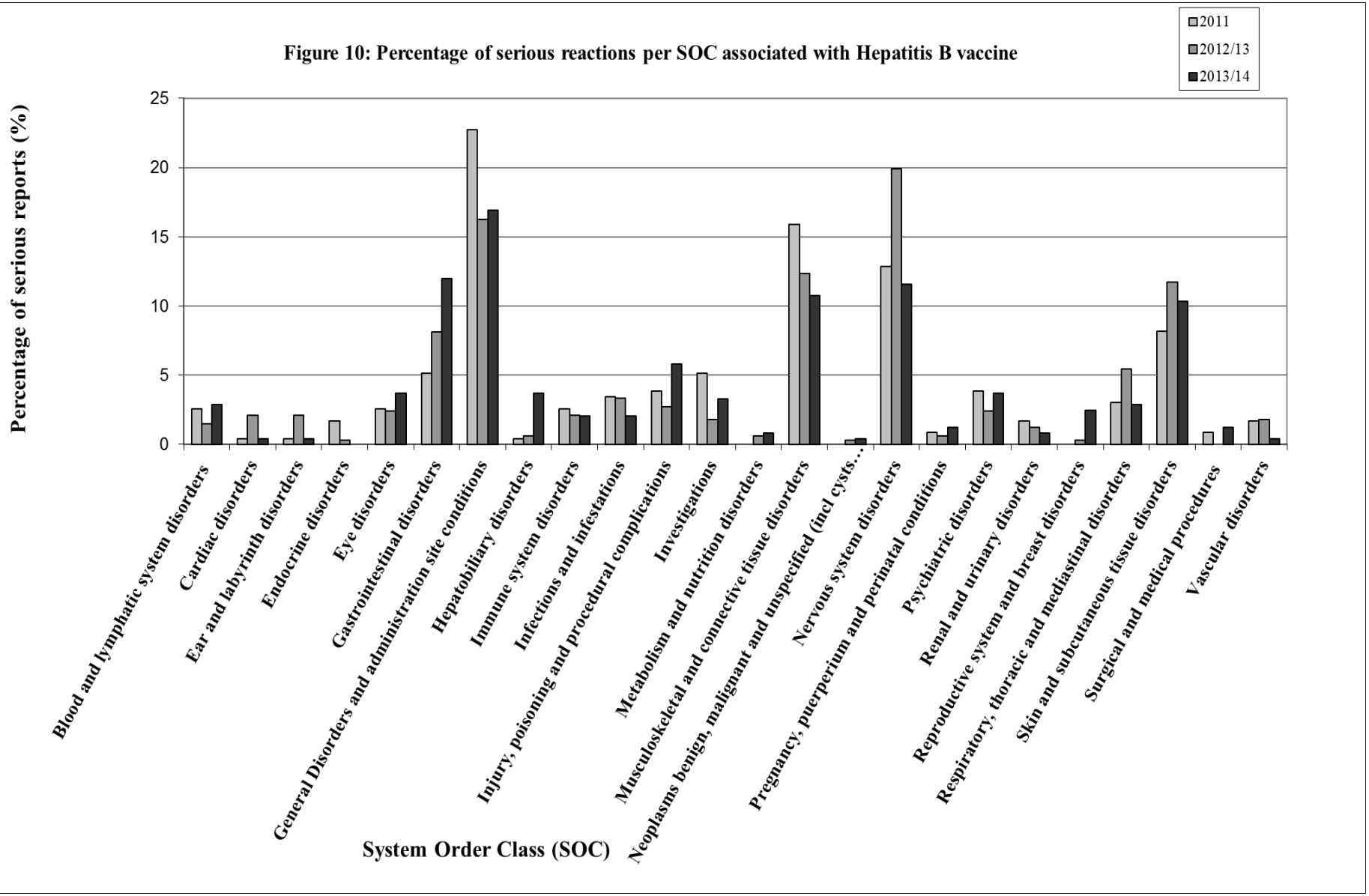
ERR = Estimated Reporting Rate
n/a Data not available at the time of writing this report.

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

The 58 serious reports were spread over 24 SOCs. The majority of reactions were in the General disorders and administration site conditions including pyrexia and injection site reactions. The other reactions concerned a wide range of isolated events which were either known rare side effects or likely coincidental with vaccination.

Conclusion: No significant new safety issues have been identified during 2013/14.

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



1.2.2. Inactivated seasonal Influenza Vaccine

Until recently influenza vaccine has mainly been 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[4]. There is also use in occupational settings. [Note: see separate section below for the childhood immunisation programme with live, intranasal vaccine; Fluenz]. Seasonal influenza vaccines used in recent years are the trivalent inactivated influenza vaccines (TIV) that contain two subtypes of influenza A and one type B virus as recommended by the World Health Organization (WHO). Last year the first tetravalent vaccine, Fluarix Tetra, containing two influenza A virus subtypes and two influenza B virus types, became available for children from 3 years of age and adults.

The total number of suspected ADRs reported in association with seasonal influenza vaccine for the last 3.5 years is shown below (table 10). These totals exclude reports in association with Fluenz which will are detailed below. In line with the other data in this report, this relates to calendar years (rather than influenza seasons). As in previous years, as a reliable estimate of all usage (routine and non-routine, NHS and private) is not available to the MHRA, exposure has been estimated simply at an upper level of 14m doses in any 12 month period. Reporting rates have remained consistently very low. Note: the 2012/13 extract period was 18 months, whereas the 2011 and 2013/14 period were both 12 months, hence the difference between denominators.

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

	2011	2012/13	2013/14
Total number of reports	459 (324)	385 (290)	534 (383)
Total number of reactions	1517 (956)	1448 (1021)	1965 (1402)
Total fatal	10	11	9
Exposure	14,000,000	21,000,000	14,000,000
ERR per 100,000 doses	3.3 (2.3)	1.8 (1.4)	3.8 (2.7)

ERR = Estimated Reporting Rate

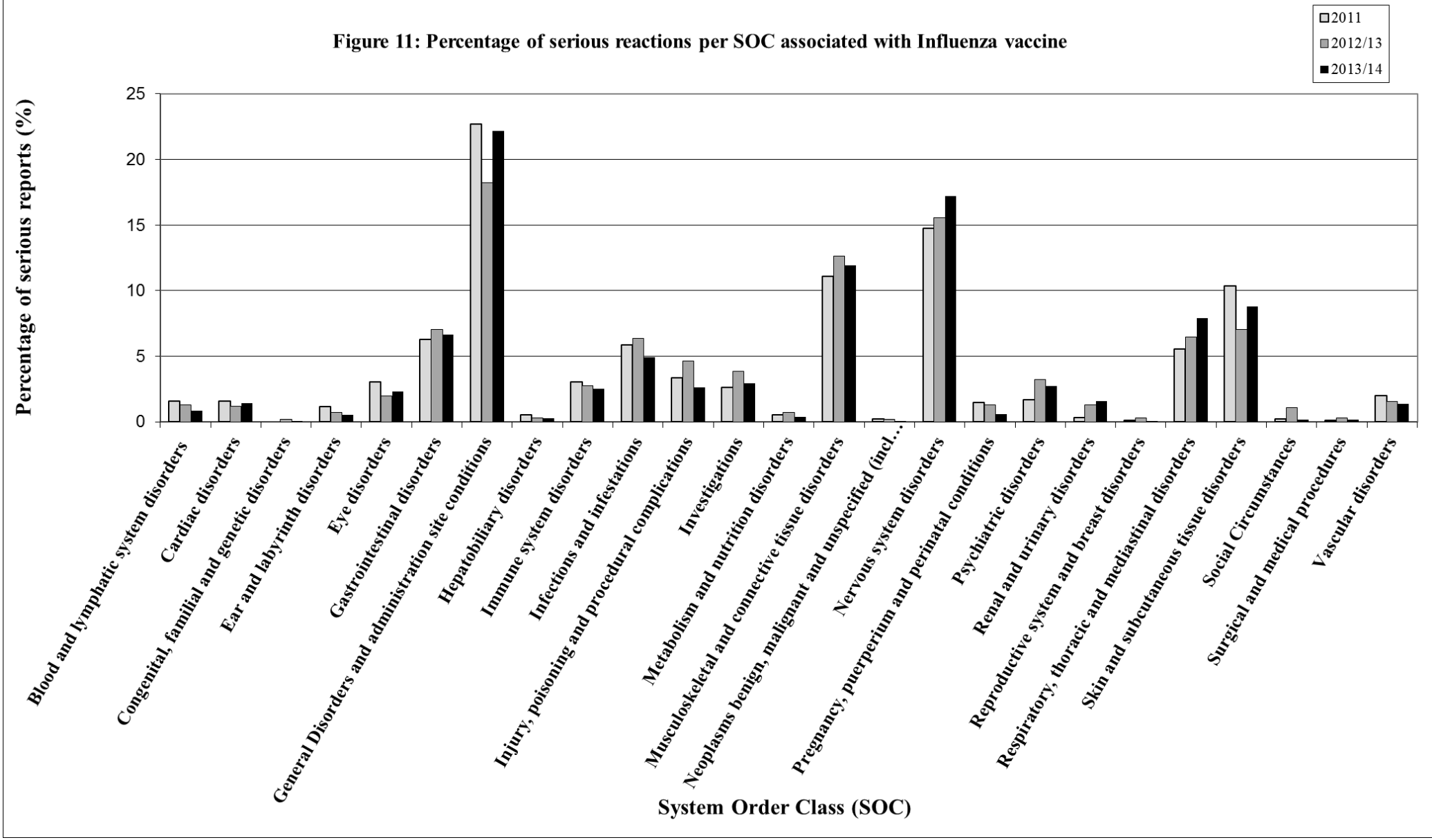
Figure 11 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three and a half years. The distribution of adverse reactions has stayed relatively constant over the last few years. The majority of reactions occurred within the 'nervous system disorder' SOC where headache and dizziness accounted for almost 30% of the reactions. The next biggest proportion of reactions belonged to the 'musculoskeletal and connective tissue disorders' SOC, where myalgia and arthralgia comprised one quarter of the reactions. These are known adverse reactions to the vaccine.

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

There were nine suspected ADRs with a fatal outcome in 2013/14. There was one case each of pulmonary fibrosis, pulmonary embolism, condition aggravated (patient had chronic lung disease of prematurity), cardio-respiratory arrest, chronic obstructive pulmonary disease, respiratory failure, ‘epilepsy, Guillain-Barre syndrome and foetal death. 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 morbidity regardless of vaccination, and background illness may be a factor.

Conclusion: No significant new safety issues have been identified during 2013/14.

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 and a half years is shown below (table 11).

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

	2011	2012/13	2013/14
Total number of reports	62 (36)	83 (59)	74 (57)
Total number of reactions	236 (158)	308 (186)	326 (262)
Total fatal	1	2	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.

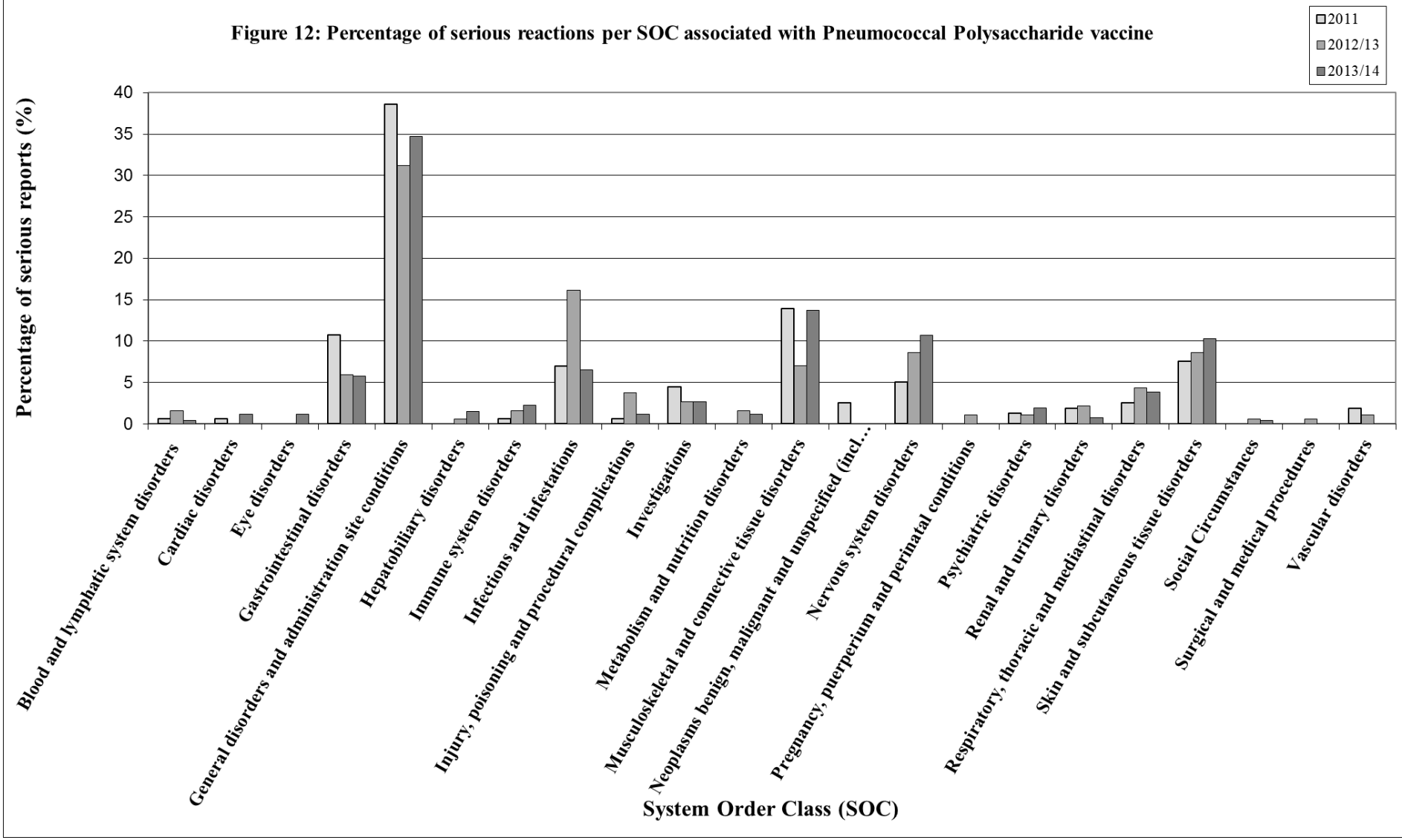
The 57 serious reports were spread over 22 SOCs as can be seen in Figure 12. Reactions in the 'Musculoskeletal and connective tissue disorders' SOC mainly include pain in extremity and arthralgia.

The majority of reactions fall into the 'General disorders and administration site conditions' SOC, including mainly injection site reactions..

Two fatal reports were received in 2013/14 associated with pneumococcal polysaccharide vaccine. One case reported 'pneumonia' and the other case, which was concomitantly administered with the influenza vaccine, reported 'pulmonary fibrosis'. A causal association with vaccination has not been established for any of these cases.

Conclusion: No significant new safety issues have been identified during 2013/14.

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 and a half years is shown below (table 12).

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

	2011	2012/13	2013/14
Total number of reports	34 (24)	23 (13)	41 (22)
Total number of reactions	69 (47)	71 (38)	112 (60)
Total fatal	0	0	2
Exposure	n/a	n/a	n/a
ERR per 100,000 doses	n/a	n/a	n/a

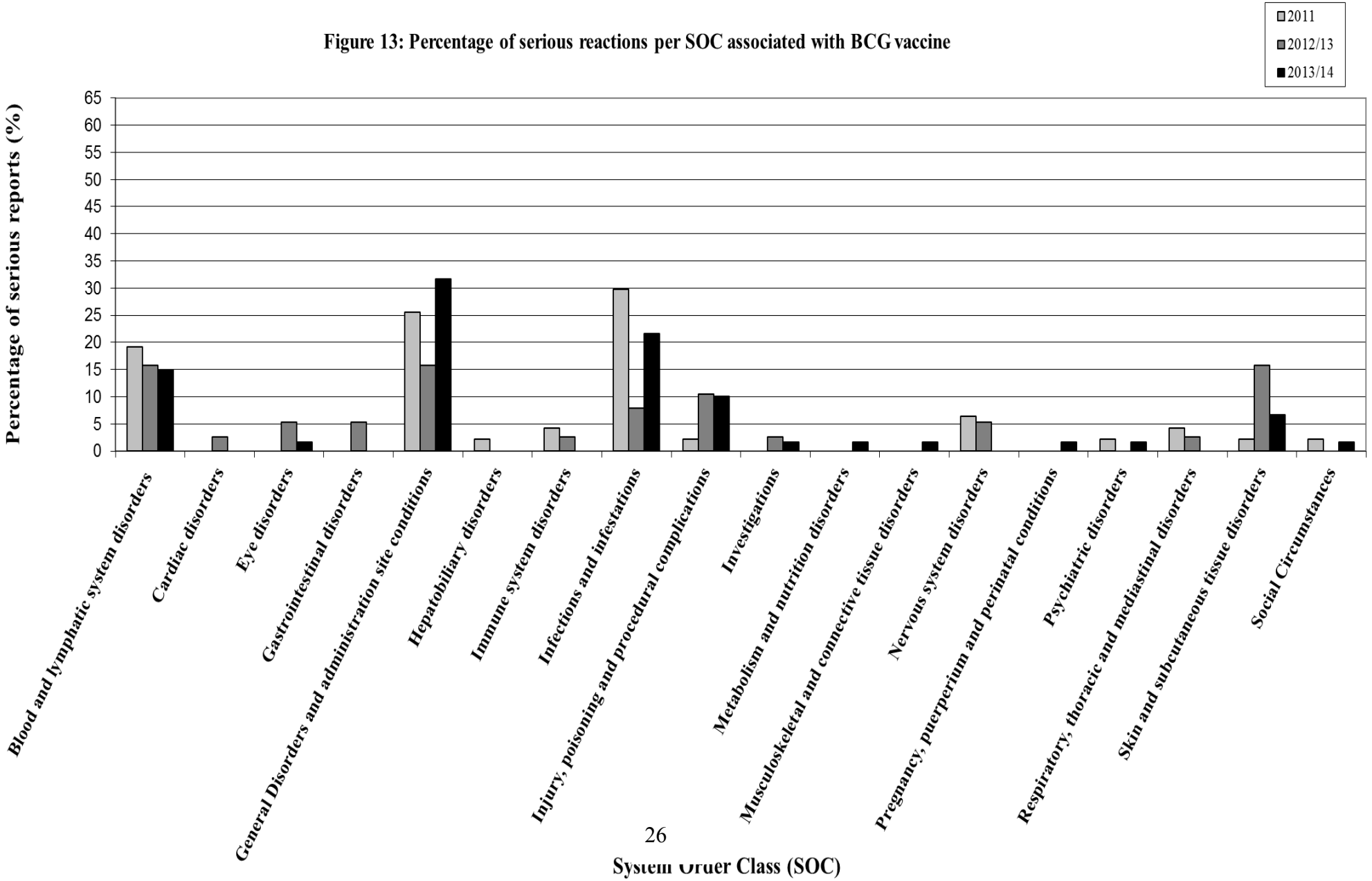
ERR = Estimated Reporting Rate
n/a Data not available at the time of writing this report.

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 for 2013/ 14 have been in the General disorders and administration site conditions and were related to injections site reactions. The remaining serious reactions related to known possible side effects of lymphadenitis and disseminated BCG infection.

There were two suspected ADRs with a fatal outcome in 2013/14: Both cases involved disseminated BCG in infants who were suspected to have been exposed to TNF-α inhibitor in utero. The use of live vaccines in infants exposed to TNF-α inhibitor is already contraindicated for 5 months following the mother's last treatment; the product information for BCG vaccine is under review.

Conclusion: No significant new safety issues have been identified during 2013/14.

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



1.2.5. Varivax and Varilrix vaccines

Varivax and Valirix are indicated for vaccination against varicella in those at risk of developing chickenpox. Since 2003, the UK recommendation includes vaccinating non-immune healthcare workers. Varicella vaccine is also recommended for healthy susceptible close household contacts of immunocompromised patients.

Table 13: Total number of Varivax and Varilrix vaccine reports (serious reports in brackets)

	2011	2012/13	2013/14
Total number of reports	4 (2)	13 (9)	20 (12)
Total number of reactions	11 (3)	30 (14)	46 (23)
Total fatal	0	0	0
Exposure	n/a	n/a	n/a
ERR per 100,000 doses	n/a	n/a	n/a

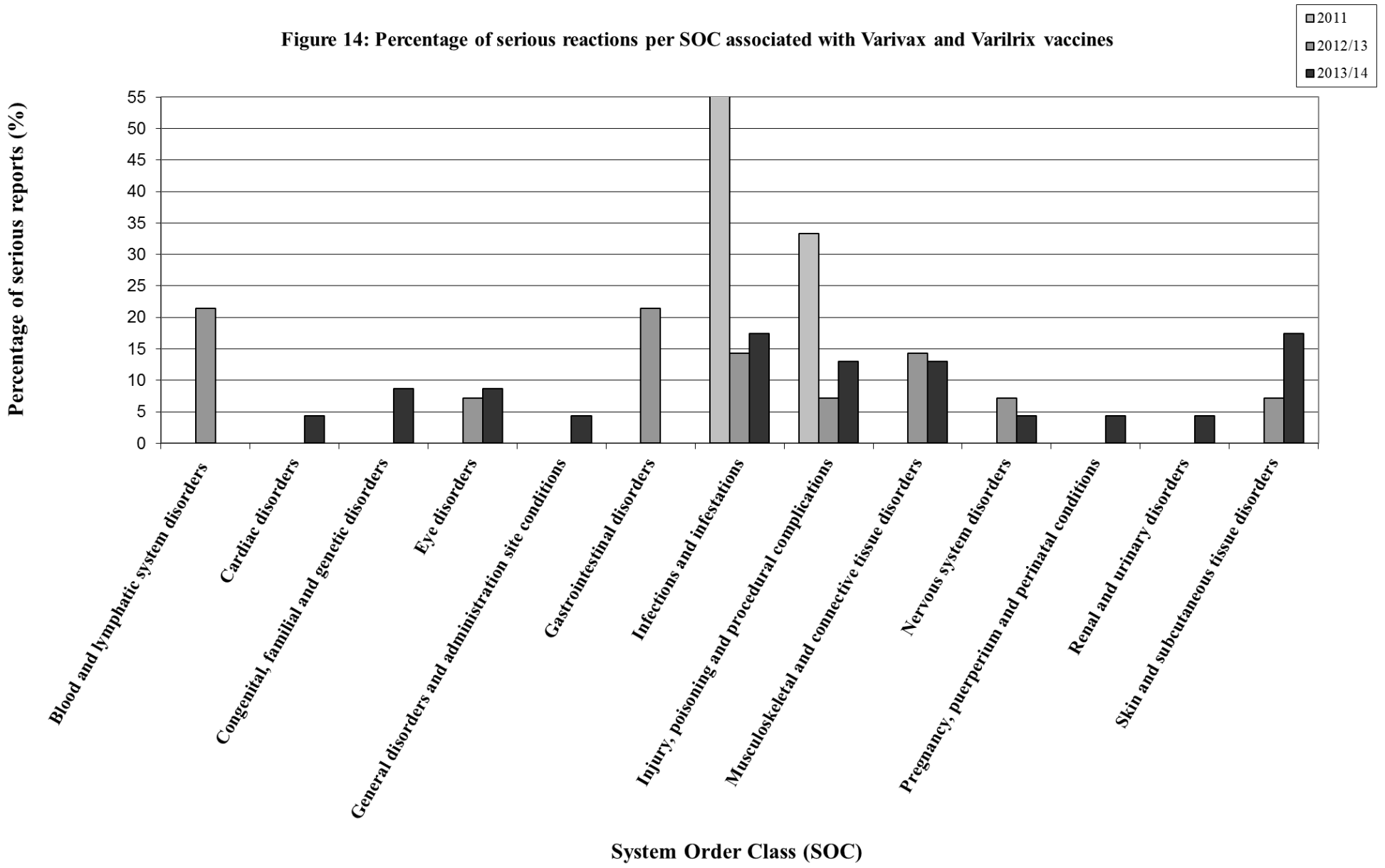
ERR = Estimated Reporting Rate
n/a Data not available at the time of writing this report.

The exposure data for the vaccine during 2013/14 were not available at the time of writing this report and as such, ERRs have not been calculated.

The reported ADRs are related to known side effects of the vaccines, and/or vaccine failure.

Conclusion: No significant new safety issues have been identified during 2013/14

Figure 14: Percentage of serious reactions per SOC associated with Varivax and Varilrix vaccines



1.2.6. Zostavax vaccines

Zostavax is indicated for prevention of shingles and post-herpetic neuralgia in those aged over 50 years. From September 2013, Zostavax has been routinely offered to patients aged 70 years, with a catch up campaign for those aged 79 years.

Table 14: Total number of Zostavax vaccine reports (serious reports in brackets)

	2011	2012/13	2013/14
Total number of reports	1 (1)	19 (17)	341 (214)
Total number of reactions	6 (3)	62 (51)	1033 (647)
Total fatal	0	0	4
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.

Exposure data for the vaccine during 2013/14 were not available at the time of writing this report and as such, ERRs have not been calculated.

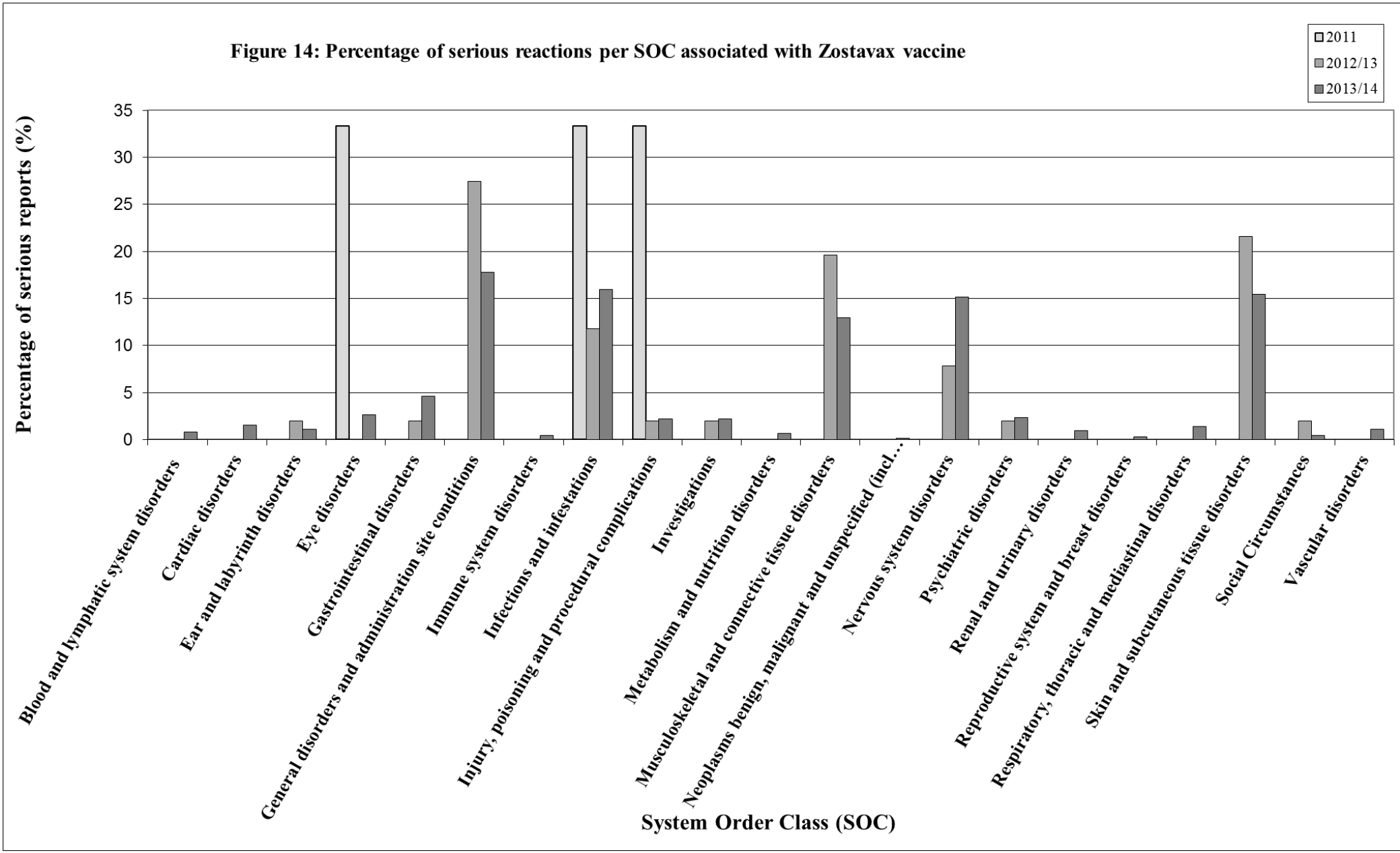
As expected, the number of reports received has increased in 2013/2014 compared with previous years due to the introduction of Zostavax routinely in September 2013. The serious reports were spread over 21 SOCs. 103 serious reactions fall within the 'Infections and infestations' SOC. This included 72 reports of herpes zoster, 3 cases of herpes zoster cutaneous disseminated and 2 cases of herpes zoster oticus. It is currently unclear if such reports may indicate vaccine-induced HZ in vaccinees, or via transmission, or whether these relate to coincidental HZ (or lack of efficacy in vaccinees). Herpes zoster and possible secondary transmission will be kept under close review.

The majority of serious events fall into the 'General disorders and administration site conditions' SOC and concerned mainly injection site reactions.

Four fatal reports were received in 2013/14. Three reports relate to myocardial infarction/heart attack and one reported multi-organ failure and death unexplained as reactions. A causal association with vaccination has not been established for any of these cases, which may relate to background illness in an elderly population.

Conclusion: No significant new safety issues have been identified during 2013/14

Figure 14: Percentage of serious reactions per SOC associated with Zostavax vaccine



1.3.1 Live, attenuated intranasal influenza vaccine (Fluenz)

Since Autumn 2013, Fluenz has been offered to all 2 and 3 year olds, as well as via several regional pilot campaigns in primary school aged children. The programme will be further expanded from Autumn 2014.

The total number of suspected ADRs reported in association with Fluenz since its introduction is shown below (table 15).

Table 15: Total number of Fluenz reports and doses distributed (serious reports in brackets)

	2013	2013/14
Total number of reports	5 (2)	366 (153)
Total number of reactions	7 (3)	923 (442)
Total fatal	0	0
Exposure	N/A	N/A
ERR per 100,000 doses	N/A	N/A

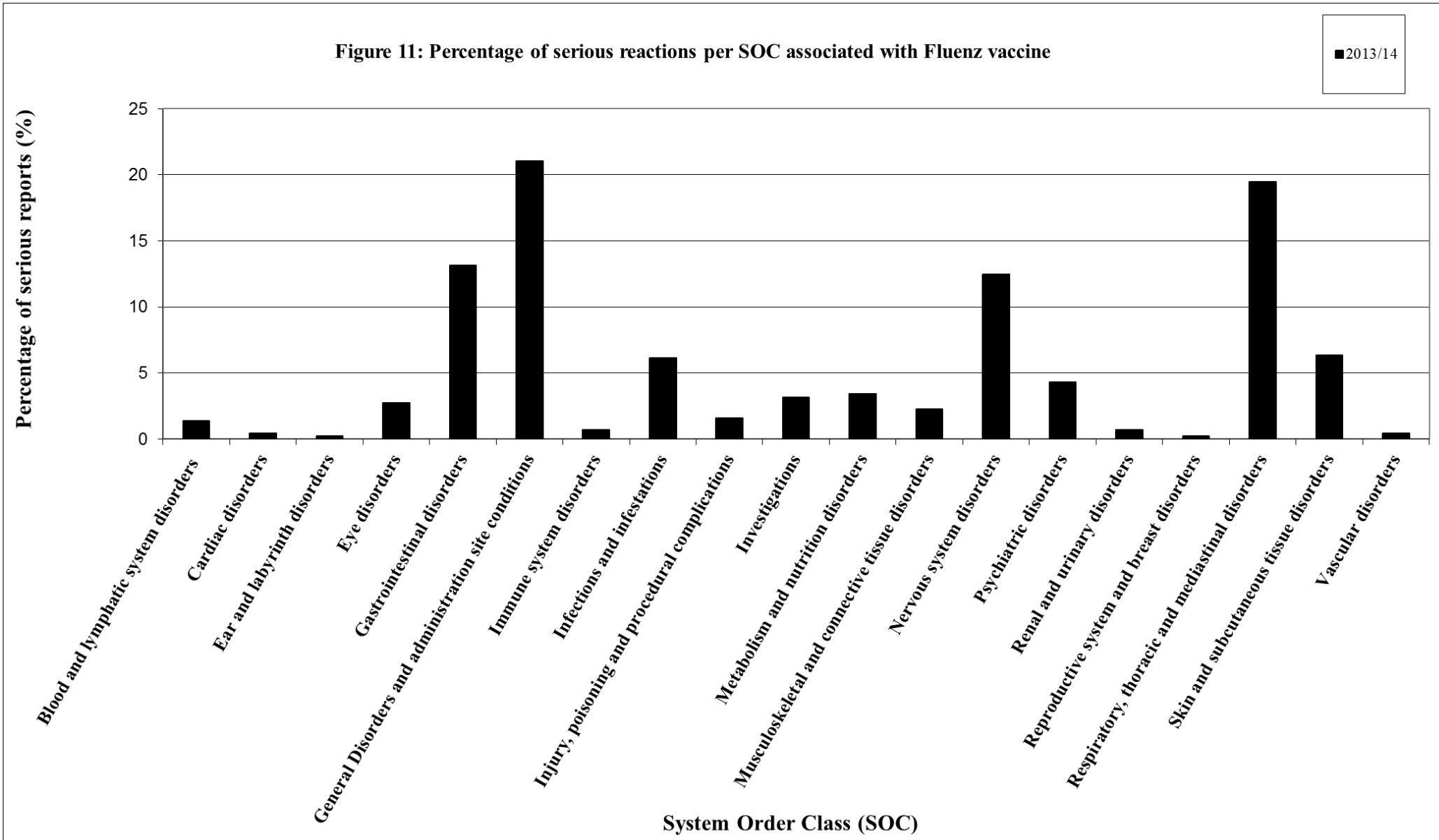
ERR = Estimated Reporting Rate
N/A Data not available at the time of writing this report.

The exposure data for the vaccine during 2013/14 were not available at the time of writing this report and as such, ERRs have not been calculated.

Figure 15 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, from 1st July 2013 to 30th June 2014. The majority of reactions occurred in the 'General disorders and administration site conditions' SOC and include reactions such as pyrexia, malaise and fatigue. These are known possible adverse effects.

Conclusion: No significant new safety issues have been identified during 2013/14

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



1.3.2 Rotarix (rotavirus) Vaccine

Rotarix was introduced to the schedule in July 2013 and protects against the most common strains of Rotavirus which is responsible for a large number of gastroenteritis related hospital admissions in young children. Rotarix is an oral vaccine and children are offered two doses before 24 weeks of age. The first dose is offered at 8 weeks of age and the second at 12 weeks.

The total number of suspected ADRs reported in association with Rotarix since its introduction is shown below. For the purpose of this report, it is assumed that vaccine uptake of 2 doses is broadly equivalent to DTaP/IPV/Hib.

Table 16: Total number of Rotarix reports and doses distributed (serious reports in brackets)

	2013/14
Total number of reports	283 (168)
Total number of reactions	728 (436)
Total fatal	2
Exposure	1,520,000
ERR per 100,000 doses	18 (11)

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

Figure (16) shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three and a half years.
The 436 serious reactions were spread over 18 SOCs. A large number of the reactions were in the Gastrointestingal disorders SOC (223). There are 48 reports of 'diarrhoea', 35 of 'haematochezia' and 25 of 'vomiting'. There were 9 reports of 'intussusception (IS)' which is a recognised, very rare risk of Rotarix. The number of reports of IS received is not greater than expected given the number of children vaccinated so far.

There were two suspected ADRs with a fatal outcome in 2013/14: 'Death' and 'Sudden infant death syndrome'. A causal association with Rotarix has not been established for any of these cases.

Conclusion: No significant new safety issues have been identified during 2013/14

Figure : Percentage of serious reactions per SOC associated with Rotarix vaccine