VACCINE-ASSOCIATED SUSPECTED ADVERSE REACTIONS REPORTED VIA THE YELLOW CARD SCHEME DURING 2006

PREPARED BY MHRA FOR THE JUNE 2007 MEETING OF JCVI

Introduction

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 between 1 January to 31 December 2006.

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 2006 and to date.

1. YELLOW CARD DATA

It should be noted that the reporting of a suspected ADR to the MHRA/CHM does not necessarily mean that the vaccine caused the condition. Other factors such an underlying or undiagnosed illness and other medications being taken may be alternative explanations.

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, there is 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 (first licensed in December 2005) from 1st January 2006 to 31st December 2006 is shown below (Table 1). Distribution data for 2006 were not available at the time of writing this report. Therefore, in order to calculate an estimated reporting rate (ERR) an assumption has been made on estimated exposure between 1 September and 31 December 2006 (i.e. 90% of 1/3 of an annual birth cohort*).

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

	Menitorix
Total no of reports	11 (6)
Total no of reactions	24 (10)
Total fatal	0
Exposure*	200,000
ERR per 100,000 doses	5.5 (3)

Table 2 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 2; Serious ADRs reported for Menitorix

Serious Suspected ADR		No of reports
Systen Organ Class (SOC)	**Preferred Term (PT)**	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	PYREXIA	1
IMMUNE SYSTEM DISORDERS	ANAPHYLACTIC REACTION	1
INFECTIONS AND INFESTATIONS	LOWER RESPIRATORY TRACT INFECTION	2
NERVOUS SYSTEM DISORDERS	FEBRILE CONVULSION	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	RASH	2
	RASH MACULAR	1
	SWELLING FACE	1
	URTICARIA	1

No new safety issues have arisen with Menitorix. Overall, the majority of the reactions were in the skin and subcutaneous tissue SOC and were signs and symptoms of injection site reactions.

The overall and serious reporting rates remain broadly similar to that of MenCC and Pediacel vaccines (see below). Given that Menitorix is a new UK vaccine, is a novel combination and has Black Triangle status (requiring ALL suspected ADRs to be reported), the number of suspected ADRs received in 2006 is reassuringly very low.

The safety experience of Menitorix since UK launch was reviewed by CHM's Biologicals and Vaccines Expert Advisory Group in February – more information on this is contained in section 2.

1.1.2 Prevenar▼ (pneumococcal conjugate vaccine)

Prevenar was introduced into the routine childhood schedule in September 2006. Prior to this time, Prevenar was recommended (from 2002) for immunisation of children aged up to 2 years at risk of complications of pneumococcal disease. It is currently recommended for use at 2 months, 4 months and around 13 months of age.

The total number of suspected ADRs reported in association with pneumococcal conjugate vaccine over the last 3 years is shown below (table 3). The distribution data for the vaccine during 2004/5 were not available at the time of writing this report and as such, ERRs have not been calculated. It is difficult to estimate exposure as since September 2006 Prevenar has been used in a catch up, as well as routine, programme. However data obtained from DH indicate that ~1.5 million doses were distributed in the UK between 4 September and 31 December 2006.

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

	2004	2005	2006
Total no of reports	9 (8)	6 (4)	325 (99)
Total no of reactions	30 (15)	16 (5)	667 (58)
Total fatal	0	0	0
Total no of doses distributed	n/a	n/a	1,500,000
ERR per 100,000 doses	n/a	n/a	22 (7)

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

Table 4 lists the serious ADRs reported in 2006. Figure 1 includes a graph of the % of serious ADRs according to organ class (SOC).

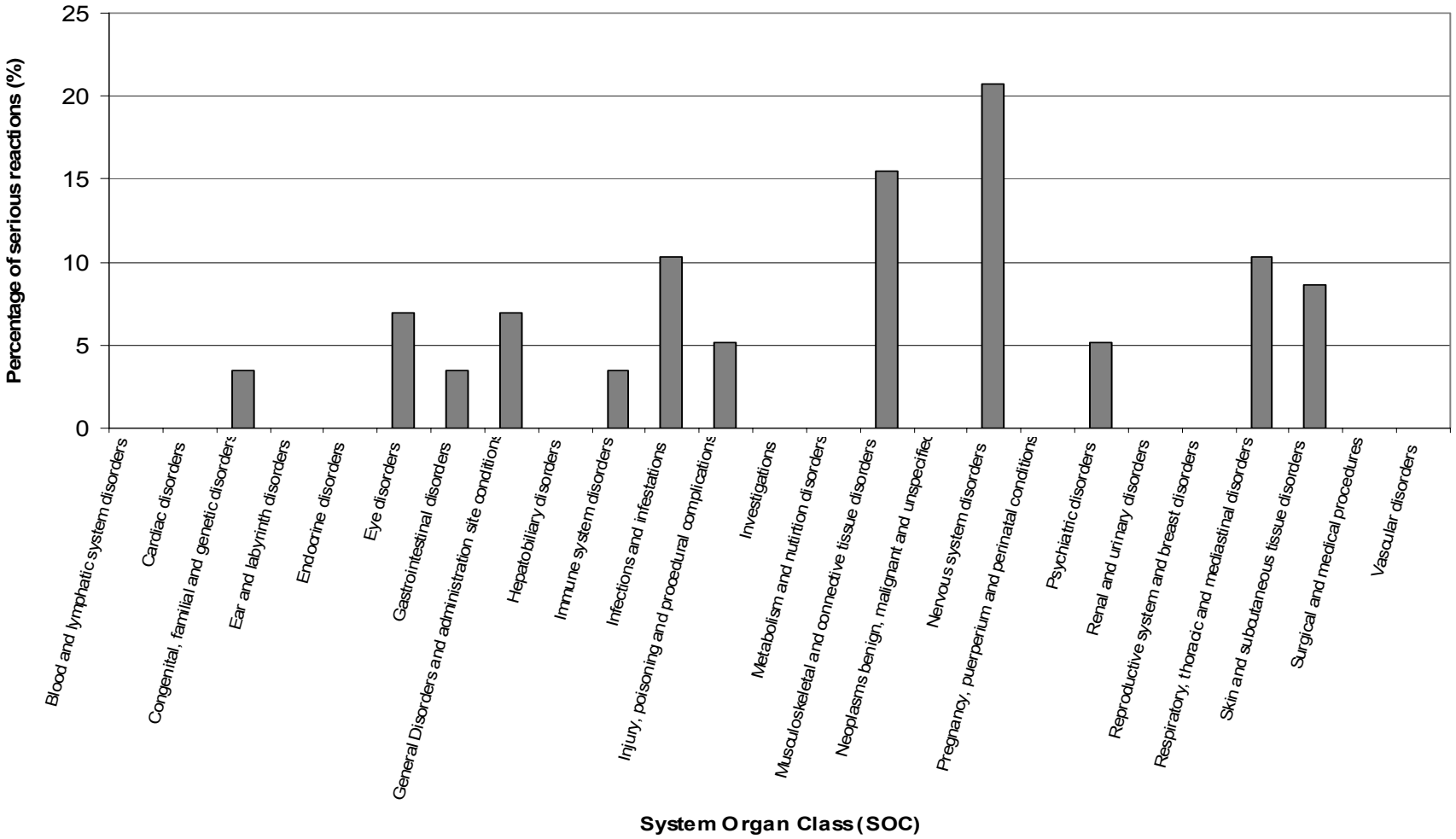
Table 4: Serious Reactions reported for Prevenar

Reaction PT	Number of reports
AMAUROSIS	1
ANAPHYLACTIC REACTION	2
ARTHRALGIA	1
BLINDNESS	1
CELLULITIS	2
CHOKING	1
CONTUSION	2
CONVULSION	2
ERYTHEMA MULTIFORME	1
EYE SWELLING	2
FEBRILE CONVULSION	7
FLOPPY INFANT	4
GRAND MAL CONVULSION	1
HALLUCINATION	3
HYPOTONIA	1
INJECTION SITE BRUISING	3
INJECTION SITE INFECTION	1
INTERCOSTAL RETRACTION	1
JOINT SWELLING	1
MASS	1

MUSCLE RIGIDITY	1
MUSCULOSKELETAL STIFFNESS	2
PLEURISY	1
PNEUMOCOCCAL SEPSIS	1
PNEUMONIA	2
PSYCHOMOTOR HYPERACTIVITY	1
PYLORIC STENOSIS	1
RESPIRATORY ARREST	1
SICKLE CELL ANAEMIA WITH CRISIS	1
SKIN EXFOLIATION	1
SWELLING FACE	3
TONGUE BLISTERING	1
VACCINATION COMPLICATION	1
VOMITING PROJECTILE	1
WHEEZING	2

No significant new safety issues have been identified to date. The vast majority of cases related to non-serious and recognised reactions. The safety experience of Prevenar since UK launch was reviewed by CHM's Biologicals and Vaccines Expert Advisory Group in February – more information on this is contained in section 2.

Figure 1: Percentage of serious reactions according to system organ class (SOC) associated with Prevenar



1.1.3 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 5).

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

	2004	*2005*	*2006*
Total no of reports	162 (104)	120 (59)	58 (34)
Total no of reactions	307 (139)	243 (47)	134 (27)
Total fatal	1	2	1
Exposure[#]	1,833,000	1,833,000	1,630,000
ERR per 100,000 doses	8.8 (5.7)	6.5 (3.2)	3.6 (2.1)

ERR = Estimated Reporting Rate

[#]Distribution data were not available at the time of writing this report. Therefore, in order to calculate an estimated reporting rate (ERR) an assumption has been made on estimated exposure based on 94% coverage and an annual birth cohort of 650,000 x 3 doses – an adjustment was made for the 2006 period to account for the switch from 3 to doses from September.

The total number of reports received in 2006 was lower than 2005 partly accounted for by the switch from a 3 to a 2 dose schedule in September 2006 and partly due to a lower reporting rate.

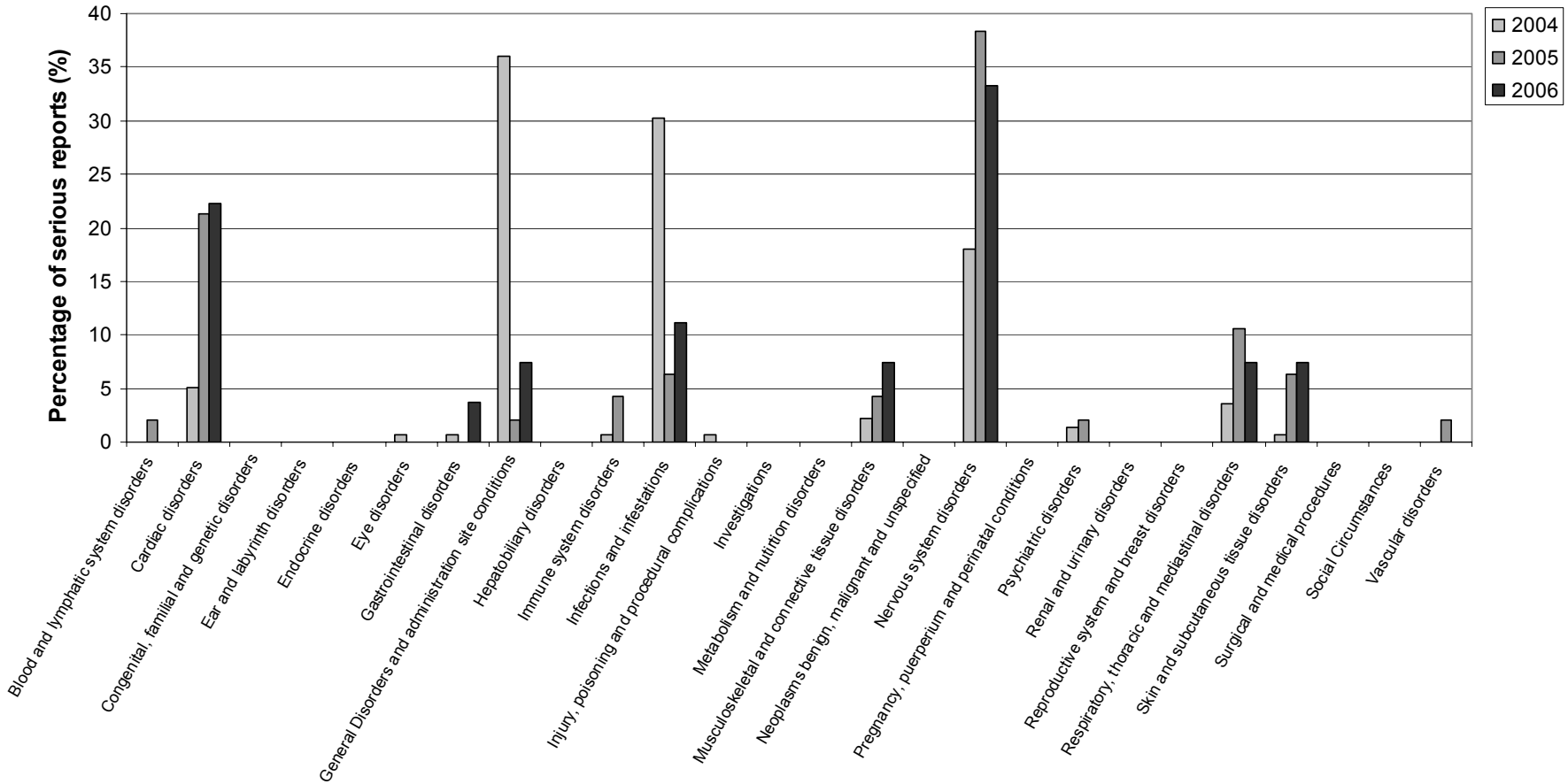
Suspected ADRs with a fatal outcome:

In 2005, 2 fatal cases; 1 of death (unspecified) and 1 of respiratory arrest.
In 2006, one case of bronchopneumonia (Co-suspected with Pediacel).

Figure 2 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last 3 years. In 2004 the SOC with the largest proportion of serious reactions was the General Disorders and Administration Site Conditions SOC (36%), however in 2005 and 2006, this was Nervous System Disorders SOC (38% and 33% respectively).

No new safety signals were identified in 2006. CHM's BVEAG reviewed the association between MenCC vaccine and nephrotic syndrome relapse in 2006 – the association was not considered causally related (see section 2).

Figure 2 : Percentage of serious reactions per SOC associated with Meningococcal Group C Vaccine



1.1.4 Pediacel▼ (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 6). The total number of ADRs reported decreased in 2006 compared to 2005 although the serious ERR remained similar. One fatal report of bronchopneumonia was reported in 2006.

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

	2004	*2005*	*2006*
Total no of reports	53 (19)	196 (65)	90 (51)
Total no of reactions	100 (13)	366 (45)	181 (36)
Total fatal	1	3	1
Exposure[#]	611,000	1,833,000	1,833,000
ERR for serious reports per 100,000 doses	8.7 (3)	10.7 (3.5)	4.9 (2.8)

ERR = Estimated Reporting Rate

[#]Distribution data were not available at the time of writing this report. Therefore, in order to calculate an estimated reporting rate (ERR) an assumption has been made on estimated exposure based on 94% coverage and an annual birth cohort of 650,000 x 3 doses - an adjustment was made for the 2004 period as Pediacel was used only from September.

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 2006 were broadly similar to those reported in the previous year. Approximately 33% of serious ADRs were neurological ADRs and largely consisted of hypotonia and cyanosis (hypotonic hyporesponsive episodes and cyanosis are recognised reactions).

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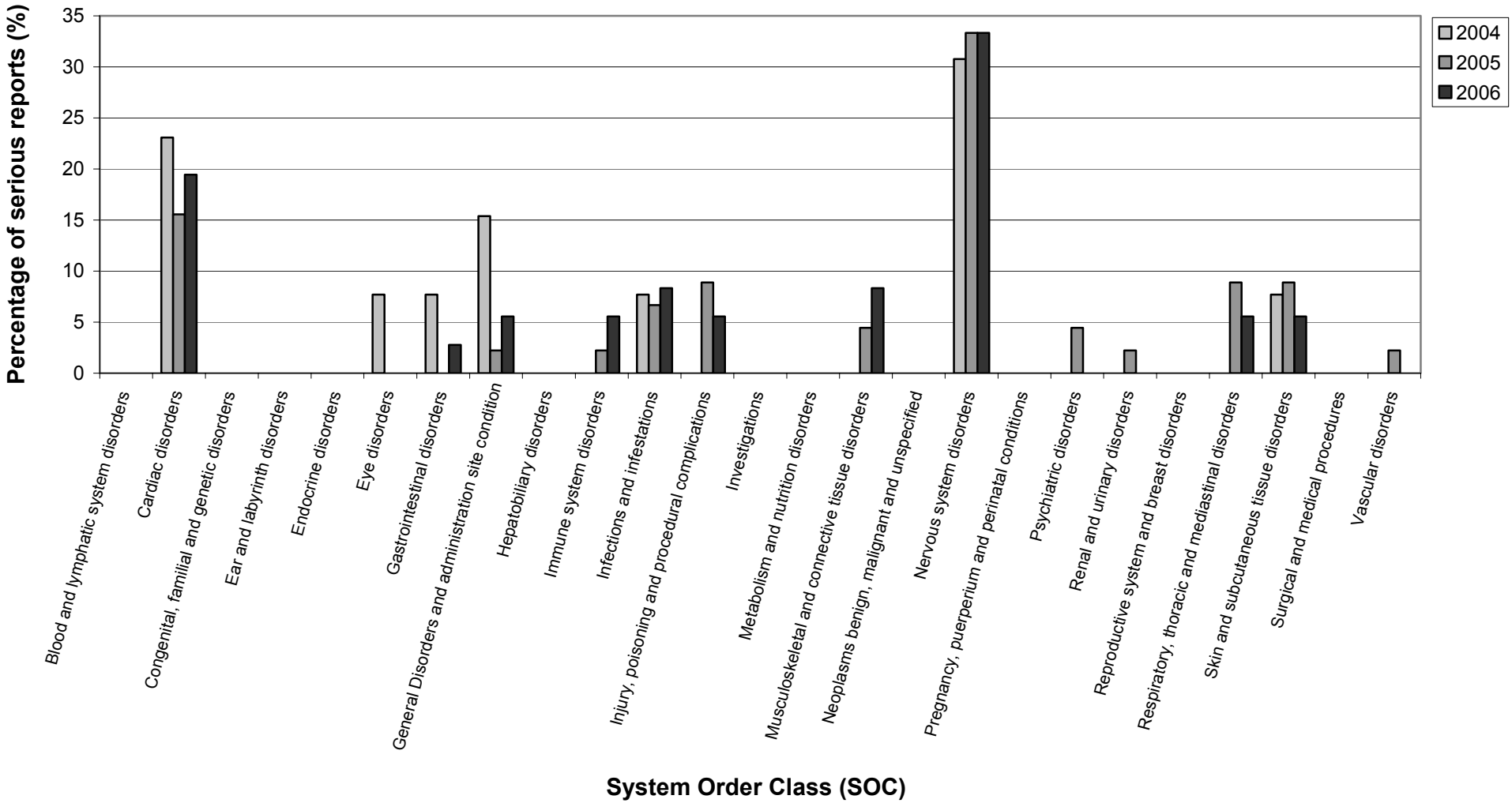
No significant new safety issues were identified during 2006.

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



1.1.5. 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 reporting rate has fallen since 2004 although the serious ERR remained similar. There have been no suspected ADRs with a fatal reaction associated with this vaccine since its launch in 2004.

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

	2004	***2005***	***2006***
Total no of reports	120 (31)	237 (66)	119 (53)
Total no of reactions	186 (23)	363 (37)	226 (33)
Total fatal	0	0	0
Exposure	203,666	611,000	611,000
ERR per 100,000 doses	59 (15)	39 (11)	19 (9)

ERR = Estimated Reporting Rate

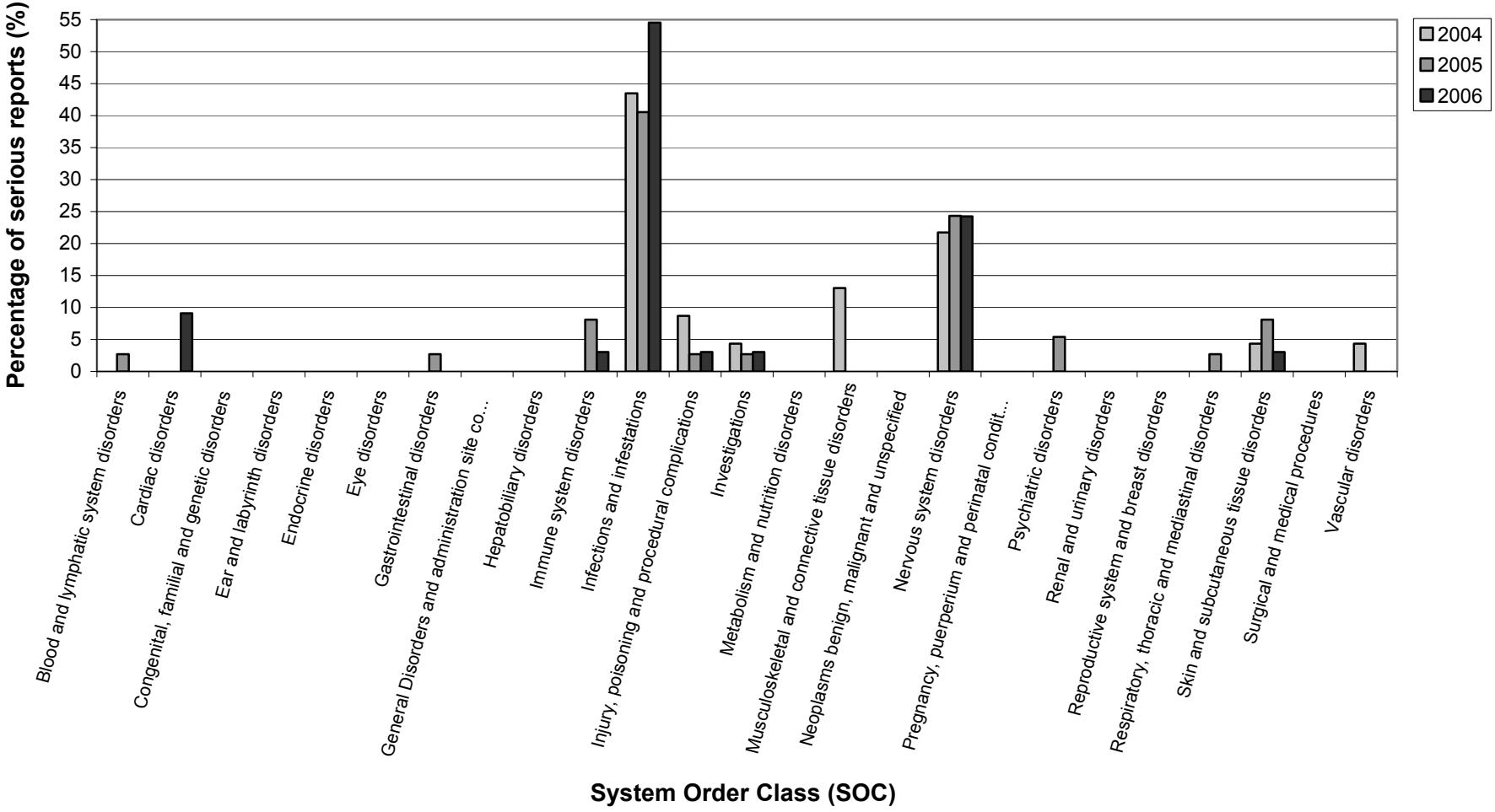
[#]Distribution data were not available at the time of writing this report. Therefore, in order to calculate an estimated reporting rate (ERR) an assumption has been made on estimated exposure based on 94% coverage and an annual birth cohort of 650,000 x 1 dose - an adjustment was made for the 2004 period as d/DTaP/IPV was used only from September.

Local reactions make up almost 90% of all (serious and non-serious) reactions reported. Figure 4 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. The majority of reactions (40-55%) relate to the infections and infestation SOC, most common reaction for the past three years has been suspected cellulitis. A further quarter of total serious reactions (8 reactions) relate to the nervous system disorders SOC.

Of all ADRs reported, most relate to injection site reactions. 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 – more details are included in section 2.

Although the data above relate to combined ADRs for Repevax and Infanrix IPV, during ongoing pharmacovigilance and reviews by CHM's BVEAG, the data for the 2 products are considered separately. **No other significant new safety issues have been identified during 2006.**

Figure 4: Percentage of serious reactions per SOC associated with DTaP/IPV vaccine



1.1.6 MMR vaccine

The total number of suspected ADRs reported in association with MMR vaccination for the last 3 years is shown below (table 7).

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

2	*004*	*2005*	*2006*
Total no of reports	105 (59)	203 (130)	130 (81)
Total no of reactions	201 (49)	418 (128)	297 (91)
Total fatal	0	0	2
Exposure[#]	1,928,780	1,105,000	1,105,000
ERR per 100,000 doses	5.44 (3.1)	18.4 (11.8)	11.8 (7.33)

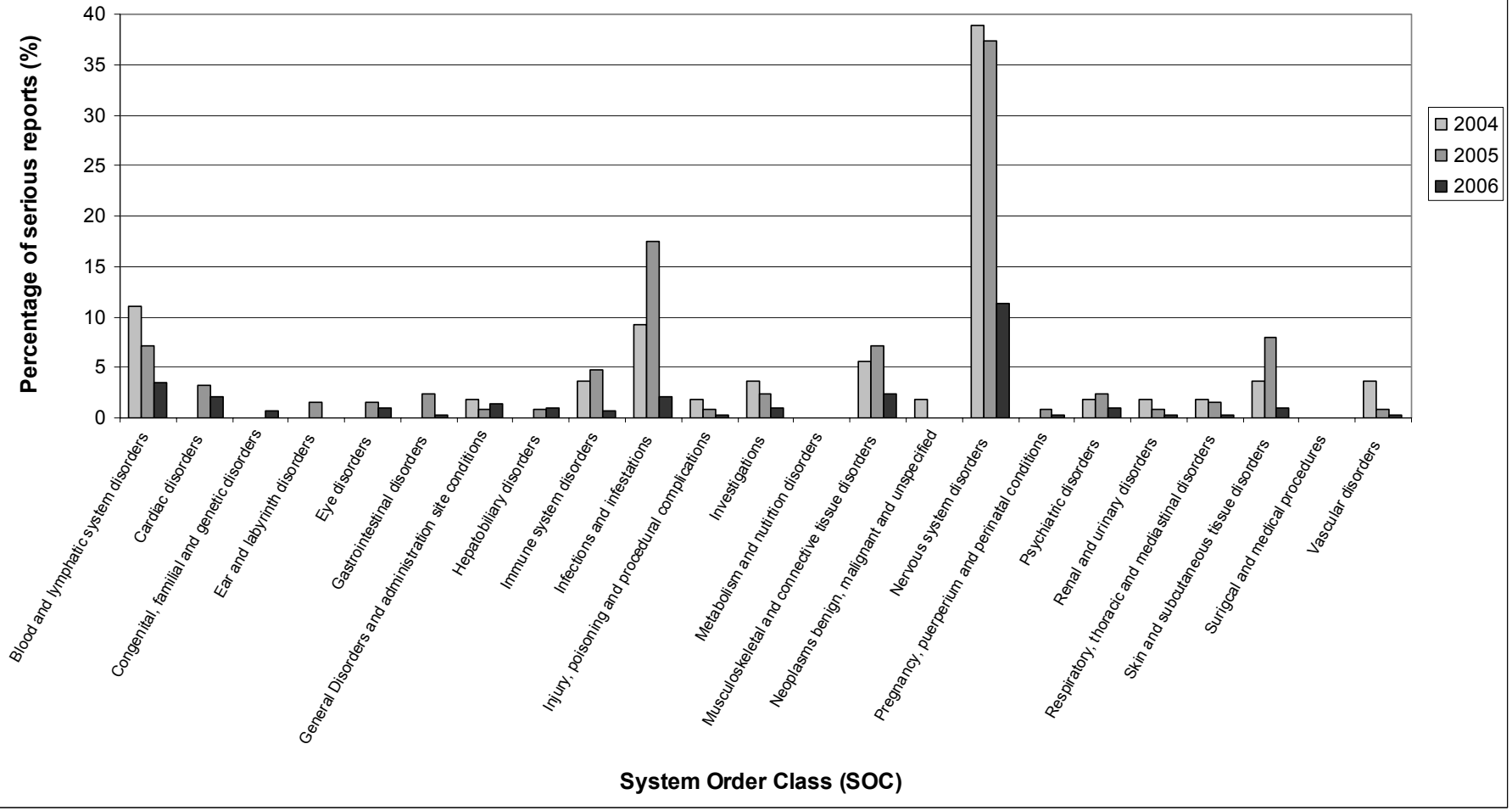
ERR = Estimated Reporting Rate

There were 2 reports with a fatal outcome during 2006: One of Still birth and one of death unexplained.

[#]Distribution data were not available at the time of writing this report. Therefore, in order to calculate an estimated reporting rate (ERR) an assumption has been made on estimated exposure based on 85% coverage and 2 annual cohorts of 650,000. It is acknowledged, however, that this may not be an accurate assumption e.g. due to usage in other age groups and possible local 'catch-up' initiatives.

Figure 5 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 reported does not appear to have changed and **no significant new safety issues have been identified during 2006.**

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



1.1.7 Revaxis (dT/IPV)

The total number of suspected ADRs reported in association with dT/IPV for the last 3 years is shown below (table 9). The total number of ADRs reported has decreased for 2006 compared to 2005. There have been no suspected ADRs with a fatal reaction associated with this vaccine since its launch in 2004.

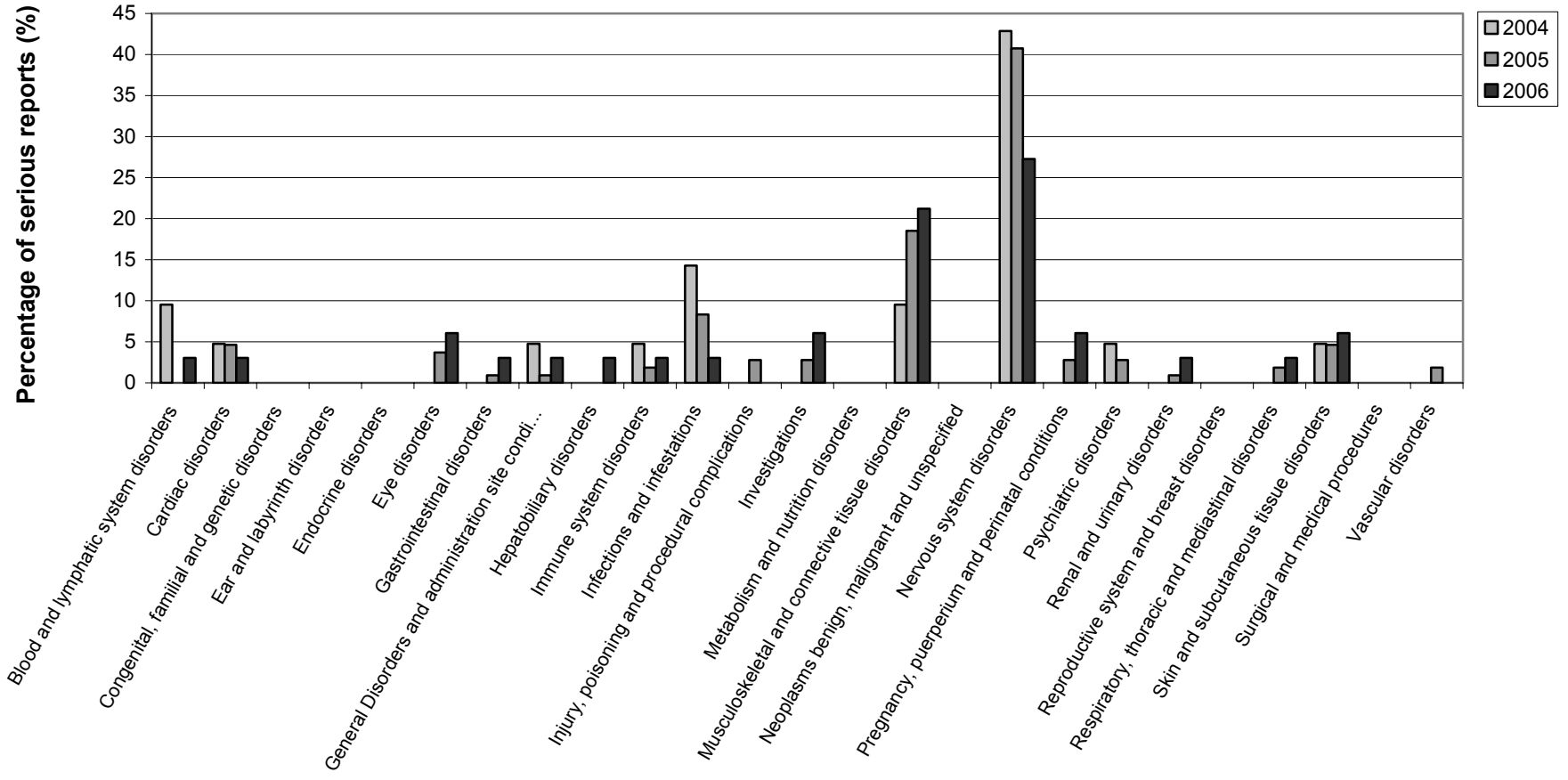
Table 9: Total number of reports and doses distributed (serious reports in brackets)

	2004	*2005*	*2006*
Total no of reports	59 (21)	177 (93)	73 (37)
Total no of reactions	145 (21)	492 (108)	198 (33)
Total fatal	0	0	0

Distribution data were not available at the time of writing this report and it is difficult to make an accurate estimation.

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 serious reactions include musculoskeletal related reactions such as myalgia and arthralgia, and nervous system disorders such as syncope and syncope vasovagal (27-43%). **There have been no significant new safety issues identified during 2006.**

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



1.2 New vaccines (non-routine)

1.2.1 Rotateq▼ and Rotarix▼ (rotavirus) vaccines

Rotarix was first authorised in February 2006 and Rotateq in June 2006 but are currently not recommended for universal use. To date we have received no UK reports for these vaccines.

Two safety issues have been identified outside of the UK in association with Rotateq – intussusception and Kawasaki's Disease. The UK is the lead EU Member State involved in assessment of this issue – more details are provided in section 2.

1.2.2 Gardasil▼ (Human Papilloma Virus) vaccine

Gardasil was first authorised in September 2006 but is not currently recommended for routine use. We have received only 1 UK report in 2006 for this vaccine to date – this was a report of dyspnoea and oral paraesthesia.

1.3 Other vaccines

1.3.1 Varivax▼ and Varilrix▼ (Varicella Zoster Virus) vaccines

Varivax was first authorised in January 2004 and Varilrix was first authorised in June 2002.

The total number of suspected ADRs reported in association with varicella zoster virus for the last 3 years is shown below (table 10). The distribution data for the vaccine was not available at the time of writing this report and as such, ERRs have not been calculated.

Table 10: Total number of reports (serious reports in brackets)

	2004	*2005*	*2006*
Total no of reports	9 (2)	13 (5)	18 (10)
Total no of reactions	13 (3)	28 (9)	71 (44)
Total fatal	0	0	1

One fatal case was reported in 2006 with the reaction Herpes Zoster.

The table below lists the serious ADRs reported in 2006.

Table 11: Serious reactions reported for Varicella Zoster Virus

Reaction PT	Number of reports
VISION BLURRED	1
ABDOMINAL PAIN	1
NAUSEA	1
VOMITING	1
CHEST DISCOMFORT	1
CHEST PAIN	1
CONDITION AGGRAVATED	2
DRUG INEFFECTIVE	2
FEELING OF BODY TEMPERATURE CHANGE	1
GAIT DISTURBANCE	1
MULTI-ORGAN FAILURE	2
PUNCTURE SITE HAEMORRHAGE	2
HERPES ZOSTER	4
CONTUSION	1
ARTHRALGIA	1
PAIN IN EXTREMITY	1
SENSATION OF HEAVINESS	2
CONVULSION	1
DYSARTHRIA	2
FACIAL PALSY	1
HEMIPARESIS	1
PARAESTHESIA	1
TREMOR	1
DISORIENTATION	1
EXPRESSIVE LANGUAGE DISORDER	1
RENAL FAILURE ACUTE	2
ASTHMA	1

DYSPNOEA	2
INCREASED TENDENCY TO BRUISE	2
PAIN OF SKIN	1
RASH GENERALISED	1
FLUSHING	1

No significant new safety issues have been identified during 2006.

1.3.2 Inactivated polio vaccine (IPV)

The total number of suspected ADRs reported in association with the inactivated polio vaccination for the last 3 years is shown below (table 12). Very few cases associated with this vaccine have been reported over the last three years, due to non-routine use.

Distribution data were not available at the time of writing this report and it is difficult to make an accurate estimation.

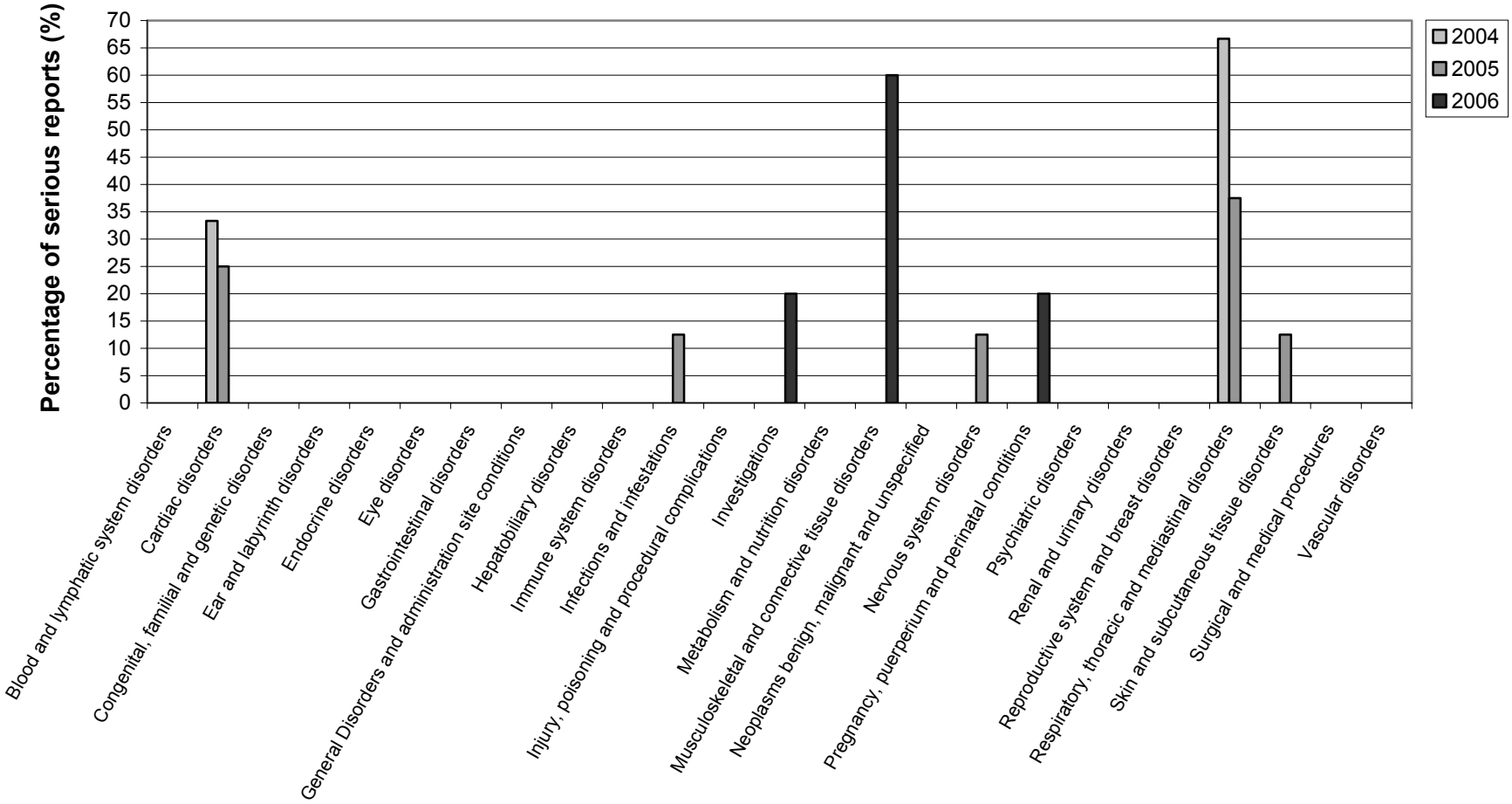
Table 12: Total number of reports and doses distributed (serious reports in brackets)

2	*004*	*2005*	*2006*
Total no of reports	4 (3)	8 (6)	2 (2)
Total no of reactions	10 (3)	22 (8)	8 (5)
Total fatal	0	0	0

The graph on the following page (Figure 7) shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years.

No significant new safety issues have been identified during 2006.

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



1.3.3. BCG vaccine

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

Distribution data were not available at the time of writing this report and it is difficult to make an accurate estimation.

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

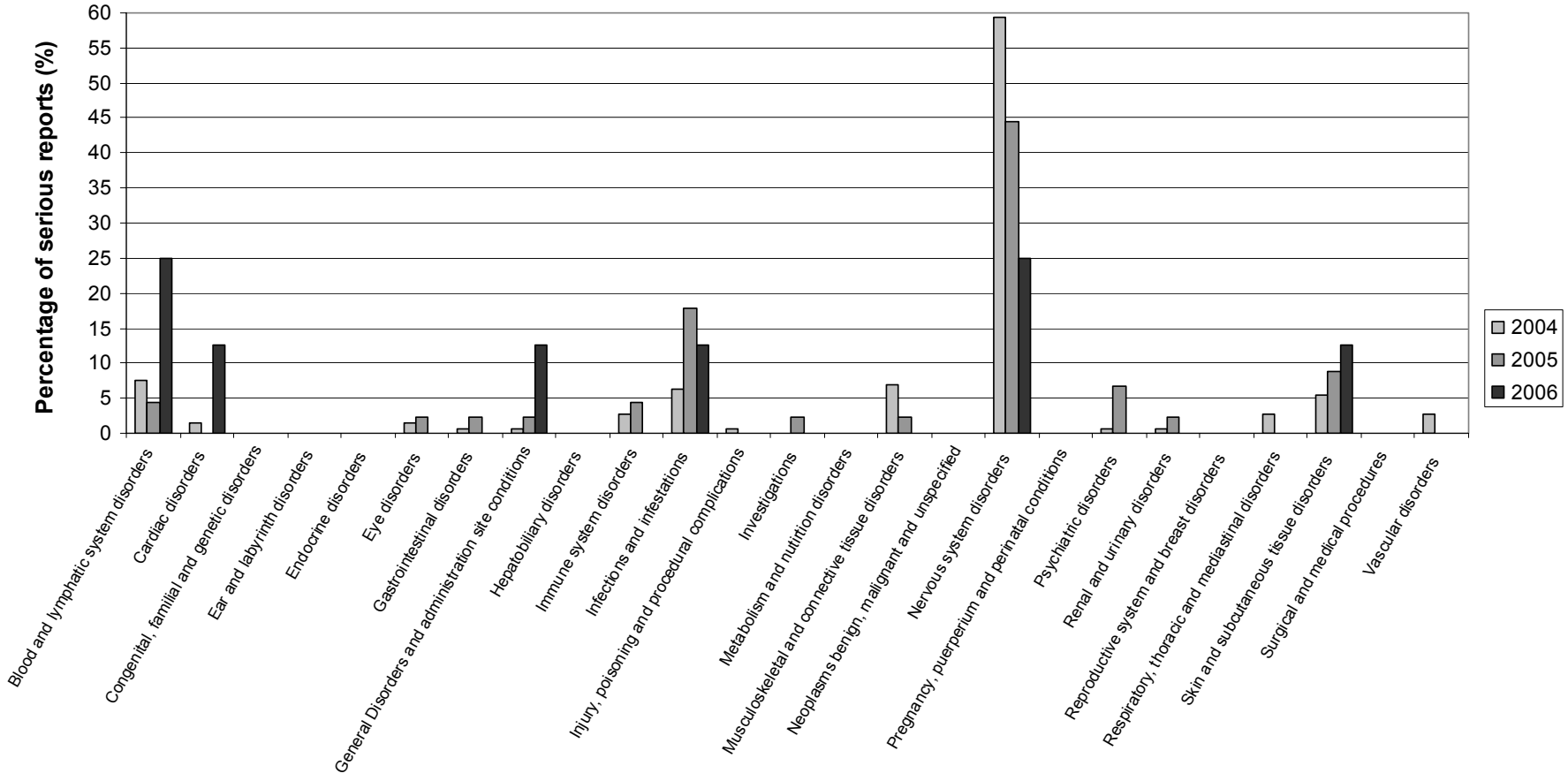
	2004	*2005*	*2006*
Total no of reports	348 (136)	330 (109)	33 (15)
Total no of reactions	650 (145)	453 (45)	40 (8)
Total fatal	0	0	1

Figure 8 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. In 2004 and 2005, the majority of serious ADRs were reported in the nervous system SOC. In 2006 only 8 serious reactions were reported and these were mainly vaso-vagal reactions and injection site reactions including abscess and associated lymphadenopathy. One case of sudden infant death syndrome was reported.

The large decrease in the number of reports of BCG in 2006 can be explained due to the fact BCG is no longer included in the schools immunisation schedule.

No significant new safety issues have been identified during 2006.

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



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

Distribution data were not available at the time of writing this report and it is difficult to make an accurate estimation.

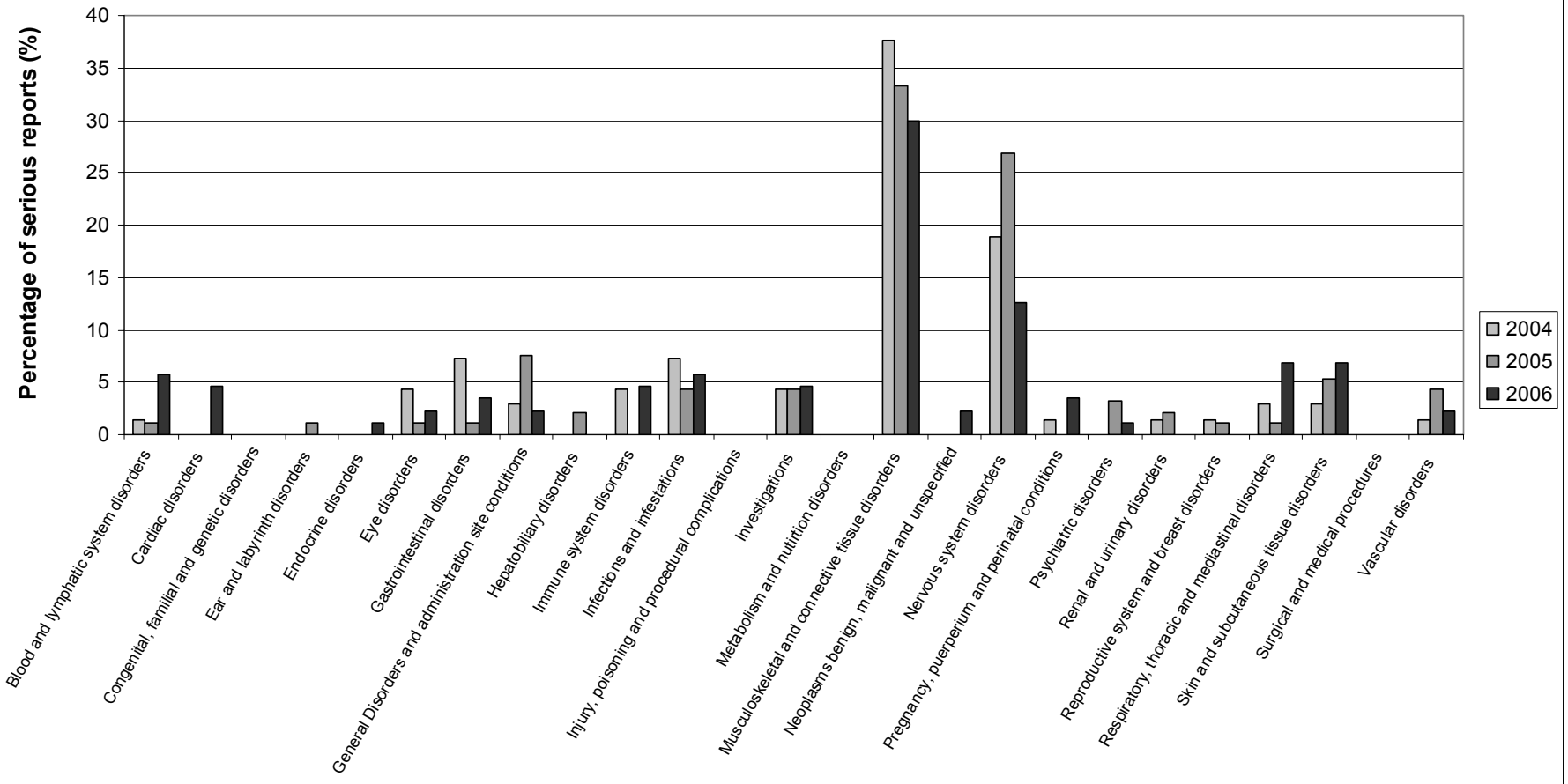
Table 14: Total number of reports and doses distributed (serious reports in brackets)

	2004	***2005***	***2006***
Total no of reports	95 (62)	103 (74)	101 (71)
Total no of reactions	260 (69)	355 (93)	337 (87)
Total fatal	0	0	0

Figure 9 shows the serious ADRs reported in each SOC, as a percentage of the total serious ADRs, for the last three years. The majority of serious reactions occurred within the musculoskeletal and connective tissue disorders SOC.

No significant new safety issues have been identified during 2006

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



1.3.5. Influenza vaccine

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

[#]Distribution data were not available at the time of writing this report. Therefore**,** in order to calculate an estimated reporting rate (ERR), it has been assumed that 14m doses were distributed during each of the last 3 years.

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

	2004	***2005***	***2006***
Total no of reports	105 (81)	112 (74)	112 (81)
Total no of reactions	253 (85)	248 (94)	317 (98)
Total fatal	4	5	3
Exposure[#]	14,000,000	14,000,000	14,000,000
ERR per 100,000 doses	0.75 (0.6)	0.8 (0.52)	0.8 (0.6)

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

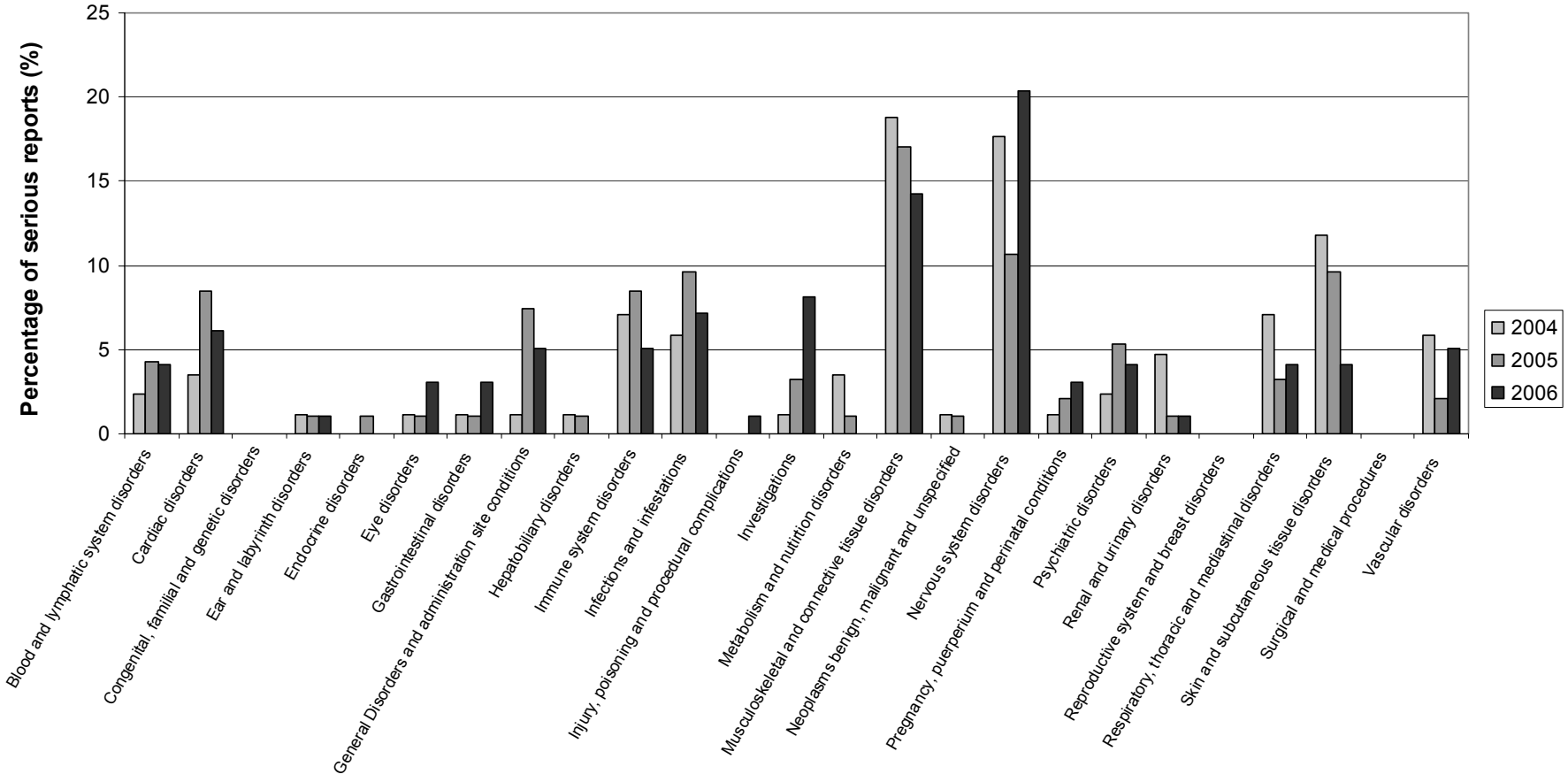
Three suspected ADRs had a fatal outcome in 2006: One case each of cardiac arrest, myocardial ischaemia and pulmonary embolism. These events were likely due to underlying illness.

Figure 10 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years.

An alleged association with Bell's palsy was reviewed by CHM's BVEAG in 2006 – further information is detailed in section 2.

No significant new safety issues have been identified during 2006.

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



1.3.6. 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 16).

Distribution data were not available at the time of writing this report and it is difficult to make an accurate estimation.

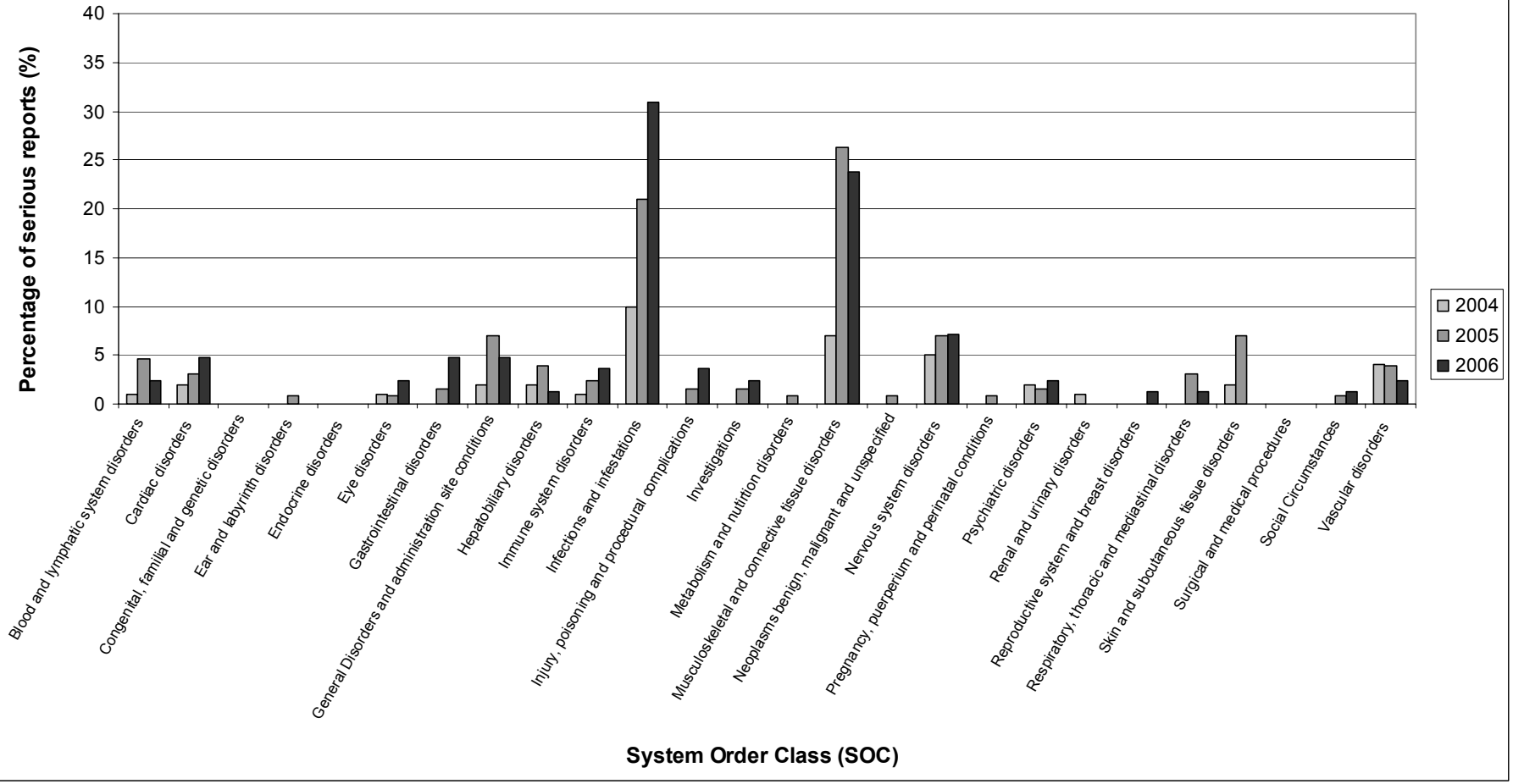
Table 16: Total number of reports and doses distributed (serious reports in brackets)

	2004	*2005*	*2006*
Total no of reports	72 (33)	231 (145)	116 (73)
Total no of reactions	145 (40)	585 (129)	341 (84)
Total fatal	3	4	1

Figure 11 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. 1 suspected ADR had a fatal outcome: asthma. The majority of reports describe local reactions. These are more frequent and more severe after repeat immunisation and product information is being strengthened accordingly.

No significant new safety issues have been identified during 2006.

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



2. KEY ISSUES CONSIDERED BY CHM'S BIOLOGICALS AND VACCINES EXPERT ADVISORY GROUP (BVEAG) AND/OR ITS PHARMACOVIGILANCE EXPERT ADVISORY GROUP (PEAG) DURING 2006 AND TO DATE.

2.1 Proactive monitoring for Pediacel

No significant new safety issues emerged from a review of the 18 month safety profile for Pediacel but the Group advised that passive ADR reporting systems are unlikely to detect differences between batches, such as those that might relate to the mouse histamine sensitisation test for residual pertussis toxin. CHM endorsed this view and recommended establishing an *ad hoc* Expert Group to better consider further options for safety assessment.

The *ad hoc* Expert Group concluded that the safety of Pediacel should be compared with whole cell pertussis in a retrospective GPRD study. A protocol for this study has been approved. They also considered that MAHs should carry out proactive studies of the response of Pediacel-primed infants to their first booster of an acellular pertussis-containing vaccines (see limb swelling issue below).

2.2 Thiomersal and neurodevelopmental disorders

B/VEAG requested that any new data relating to the alleged association between thiomersal in vaccines and neurodevelopmental disorders be kept under close review. Accordingly, the Group has assessed newly published data 3 times since May 2006. The majority of new evidence comes from studies by Geier and Geier, who have used similar methods to those previously used and which have been robustly criticised by CHM. An additional study by Fombonne concluded that the prevalence of autism in Quebec did not correspond in time with changes in the levels of thiomersal in vaccines and with MMR uptake. While the Group considered this to be a more robust study than those by Geier and Geier, it was still based on ecological methods and therefore subject to confounding and unable to evaluate causality. The Group concluded that the findings of these studies did not alter the current position for no causal association.

2.3 Men CC vaccine and nephrotic syndrome relapse

In contrast to an earlier study that resulted in a warning being added to product information for MenCC vaccines, a subsequent population-based study found no evidence for an increase in the incidence of nephrotic-syndrome relapse post vaccination with Men C. The Group considered that the more recent study was metholodigically sound and, unlike the previous study, had been designed to specifically investigate this alleged association. The Group concluded that this study appeared to refute an association but that the warning should remain in the SPC until sufficient experience in the older population was gained with Menitorix.

2.4 Influenza vaccine and Bell's Palsy

Existing evidence from a case-control study provided no evidence for an association between the intramuscular/subcutaneous administration of influenza vaccine and Bell's palsy (in contrast to intranasal administration) but spontaneous data showed weak evidence for an association. The Group considered that a newly published self-controlled cases series study provided robust evidence for no causal association between intramuscular/subcutaneous influenza vaccine and Bell's palsy.

2.5 Menitorix and Prevenar – Pharmacovigilance plans

BVEAG considered the pre-licensing safety data for Menitorix (MenC/hib) and Prevenar (pneumococcal conjugate) and endorsed the MHRA's proposals to implement a number of enhanced Pharmacovigilance measures following the their introduction of these vaccines into the routine childhood immunisation schedule.

A review of the first 6 months safety experience of these vaccines was considered by BVEAG in February 2007 – the Group agreed that no new safety issues had been identified.

2.6 Pandemic flu vaccines

BVEAG have been updated on key developments within Europe for the post-marketing evaluation of pandemic vaccines. National pharmacovigilance plans have been developed by MHRA and we will continue to work closely with EU Member States, EMEA and the EVM on further developing such EU plans.

2.7 Extensive limb swelling with DTaP-containing boosters (Repevax and Infanrix IPV)

MHRA placed a statement on its website in 2005 (see attachment) reminding prescribers of the known risk of extensive limb swelling following 4th and 5th doses of DTaP-containing vaccines. This followed a review of available data by MHRA and unfounded concerns amongst UK health professionals about contaminated batches. Many cases of children being possibly misdiagnosed with cellulitis and inappropriately hospitalised and/or treated with antibiotics have been reported to MHRA.

Given that there will likely be an increase in incidence of such reactions later in 2007 when the first cohort of children fully primed with Pediacel presents for Repevax/Infanrix IPV, MHRA has asked the manufacturers of these vaccines to study the incidence of such reactions in order to better inform prescribers. MHRA is currently discussing a protocol with the manufacturers.

2.8 Infant immunisation and apnoea

The issue of apnoea following infant immunisation has been under review via the EMEA since 2002. This review concluded in January 2007. The key conclusions were:

- For healthy terms infants there is no clear evidence of a risk and no basis for regulatory action
- For premature infants, particularly those ≤30 wks gestation and under 3 months of age, there is an increased risk within 48 hours of immunisation. The recommendation was that all infant vaccines should carry a relevant warning

The MHRA agreed with the broad conclusions although expressed concern over the practicality of the precise wording to be included in the product information. The particular concern was that advice to 'monitor' infants for 48 hours after immunisation would create practical difficulties for infants already discharged from hospital. However, the majority of other Members States considered that the wording 'monitor' should be included in the product information but this should be 'appropriate to the level of risk' to allow flexibility in interpretation of the advice at national level.

Following further discussion at EMEA, the following draft wording was adopted for inclusion in the prescribing information for any EU vaccine possibly used in premature infants – this is currently out for consultation with manufacturers:

SPC Section 4.4:
The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity.

As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

SPC section 4.8:
Apnoea in very premature infants (≤ 28 weeks of gestation) (see section 4.4)

2.9 Rotateq vaccine – intussusception and Kawasaki's disease

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

No serious safety concerns were identified in pre-licensing studies that included approximately 70,000 infants for RotaTeq and 60,000 infants for Rotarix. The most commonly reported adverse reactions were diarrhoea, vomiting, irritability and fever.

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

Post-marketing surveillance studies are underway to further evaluate the safety of both vaccines and intussusception is one of the primary outcome measures.

Since the approval of these vaccines in Europe two safety issues have been raised in association with RotaTeq – intussusception and Kawasaki's disease. We are not aware of any safety concerns with respect to Rotarix; however, Rotarix has so far

been used in countries whose Pharmacovigilance systems are likely to be less well developed than the US and Europe.

2.9.1 Intussusception and RotaTeq

In February 2007 the FDA announced that the Vaccine Adverse Event Reporting System (VAERS) had received 28 spontaneously reported cases of non-fatal intususception in association with 3.5 million doses of RotaTeq distributed (approximate reporting rate of 0.04 per 5000 doses). They advised that this number of cases does not exceed the number expected based on background rates (1-2 per 5,000 per year) for an unvaccinated population of children aged 6 – 35 weeks. Nevertheless, the US prescribing information has been updated to include this information.

These cases have been carefully considered by UK and European Expert Advisory Groups, who concluded that they are not suggestive of a causal association with RotaTeq vaccination. Thus, there does not appear to be the same clustering of cases with respect to time since vaccination that was clearly observed following vaccination with Rotashield and the observed reporting rate is low relative to the expected incidence in this age population.

However, the company has been asked to provide further information about the measures that are in place for monitoring intussusception in the post-marketing environment.

Since the FDA's announcement in February the MAH has received a further 67 reports of intussusception. However, these are likely to be the result of stimulated reporting on the back of the publicity that was generated in February 2007. No further action has been taken by the FDA.

2.9.2 Kawasaki's Disease and RotaTeq

In the Phase III safety study (REST) for RotaTeq, 3 cases of Kawasaki Disease (KD) were reported in the vaccine arm versus none in the placebo arm. At the time, this was not considered to be a safety signal but a further 2 cases have since been unblinded, both of which occurred within the RotaTeq arm.

Expert advice based on further clinical details of the cases suggests that all 5 cases are Kawasaki's disease. In addition, one case that was originally reported to be Kawasaki-like vasculitis was subsequently confirmed as classic KD – this case occurred in the placebo arm. All 6 cases of KD occurred within 30 days of vaccination and in infants under the age of 6 months. The risk difference for KD between the Rotateq and placebo arms is not statistically significant but the limited power of the study for this endpoint means that a 3 fold increased risk cannot be excluded.

Observed/Expected (O/E) calculations provided by the MAH found that the observed incidence of KD in the RotaTeq group was no higher than expected (whilst in the placebo group 5 times fewer cases occurred than expected). These estimates were at odds with those of the MHRA who calucated that there could be up to 5 times as many cases of KD in the RotaTeq arm as would be expected in that age group. This discrepancy stems from using different time-at-risk periods for the observed KD incidences. The MAH has been asked to urgently clarify their calculations.

No other cases of KD have been reported to the MAH despite the use of more than 3.5 million doses of RotaTeq in the US. However, this observation should be treated with caution as healthcare workers may not be expected to make a connection between KD and RoatTeq in the absence of a prior hypothesis.

Although further evaluation of this signal is necessary, the MAH will be asked to add the REST study findings to RotaTeq product information. The FDA has informed us that they also intend to update their Prescribing information. Since a causal association between RotaTeq and KD has not yet been determined it will be essential that any communications are balanced and do not cause unnecessary alarm. Further evaluation of a possible relationship between RotaTeq and KD in post-marketing studies will also be necessary.

The rapporteur for Rotarix is currently investigating whether a similar signal for KD may also exist.

2.9.3 Conclusion

Currently there is insufficient evidence to confirm a causal association between RotaTeq and intussusception or Kawasaki's disease. However, in view of the serious nature of these conditions, both intussusception and KD will be further evaluated by careful analysis of spontaneous reporting data and post-marketing surveillance study findings.

On the data that are currently available the balance of benefits and risks for RotaTeq and Rotarix remains positive.

Prepared; June 2007

[redacted]

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

ANNEX

Local reactions associated with pre-school d/DTaP-IPV boosters

Extensive limb swelling following d/DTaP IPV boosters is common but transient

Acellular pertussis replaced wholecell pertussis in DTP[1] vaccines[2] (DTaP and DTwP respectively) in the UK immunisation programme in September 2004[3]. The current immunisation schedule consists of a primary series of DTaP/IPV/Hib (Pediacel) vaccine at 2, 3, and 4 months of age and a pre-school booster dose of either dTaP/IPV[4] (Repevax) or DTaP/IPV (Infanrix IPV) at 3 years 4 months to 5 years of age. Vaccines containing acellular pertussis[5] are generally less reactogenic than those containing whole cell pertussis[6], particularly in older children.

It is recognised, however, that booster doses of vaccines containing acellular pertussis are associated with an increased risk of injection site reactions[7,8], some of which affect the entire limb, compared to primary vaccination. The risk appears to be dependent on the number of prior doses of DTaP vaccine, with a greater risk following the 4 th and 5th doses. However, such reactions to a DTaP booster may also occur in children who have been primed with one or more doses of a DTwP vaccine. Injection site reactions can also occur following any injection procedure and any injected vaccine, irrespective of immunisation history.

Children in the UK will not begin to routinely present for a 4th consecutive dose of a DTaP vaccine (as **d**TaP/IPV or **D**TaP/IPV) until late 2007. However, as DTaP (Infanrix) vaccine has been periodically used in the UK infant primary series since late 1999 when DTwP vaccines were in short supply, many children presenting for pre-school boosters since mid 2003 may already have received at least one dose of DT **a**P. It is therefore possible that some children presenting for Infanrix IPV or Repevax boosters may be at an increased risk of experiencing an injection site reaction, depending on the types of DTP vaccine received in infancy.

A review of UK Yellow Card data associated with Infanrix, Infanrix IPV and Repevax boosters has shown that reports of extensive local reactions have been received at a rate of ~15-20 reports per 100,000 children vaccinated. Due to under-reporting this is likely to underestimate the true incidence of such reactions.

Cases of local reactions reported in the UK have ranged from redness and swelling up to several inches around the injection site to swelling from shoulder to elbow. Several cases have presented with blistering around the site of swelling. In up to 20% of cases of extensive local swelling the children have been given systemic antibiotics in the absence of obvious laboratory or other evidence of infection. Data would indicate that antibiotic treatment or the use of anti-inflammatory medicines have no effect on the duration or severity of the reaction compared with no treatment. Several cases have also reported a presumptive diagnosis of cellulitis. Based on the information available, it is assumed that, due to unfamiliarity with this kind of local reaction, these cases have been diagnosed and treated as infection as a precaution.

Cases of extensive limb swelling following DTaP boosters usually develop within 24 hours of vaccination and recover, without sequelae, within ~5 days. Such reactions do not contraindicate further doses of DT or DTaP vaccine. If a child presents with signs of extensive limb swelling following d/DTaP-IPV pre-school vaccination, it is important to carefully consider whether this may be a recognised injection site reaction or whether there are any signs of infection.

1 diphtheria, tetanus and pertussis
2 this was accompanied by a switch from use of live oral polio (OPV) vaccine to inactivated polio vaccine (IPV)
3 www.dh.gov.uk/assetRoot/04/08/73/47/04087347.pdf
4 d_TaP refers to low dose diphtheria
5 including DTaP in combination with other antigens
6 Jefferson *et al*. Vaccine 2003; 21: 2003-14
7 Gold et al. Medical journal of Australia 2003; 179:191-194
8 Rennels et al. Pediatrics 2000; 105(1)