VACCINE-ASSOCIATED SUSPECTED ADVERSE REACTIONS - 2004

The data on suspected adverse reactions (ADRs) for each year included in this report are taken from the adverse drug reaction on-line information tracking (ADROIT) database using the extract dates 1 January to 31 December. It should be noted that the reporting of a suspected ADR to the MHRA does not necessarily mean that the vaccine caused the condition. Other factors such an underlying or concurrent illness and other medications being taken may be alternative explanations.

Exposure data are based on estimated distribution data for each fiscal year. Data are not provided on the exact number of vaccinees immunised within each year. Please note that exposure data for hepatitis B vaccines are based on sales data provided by Aventis Pasteur MSD and GlaxoSmithKline and are commercially confidential.

The DTaP+Hib (Infanrix Hib) vaccine is no longer in use and very few cases of suspected ADR reports were received in 2004. In summary, a total of 5 reports including 6 ADRs (4 serious) were received. No new safety issues were identified. For this reason DTaP+Hib will not be discussed further in this paper.

1. New Vaccines (Pediacel, Repevax and Revaxis)

The total number of suspected ADRs reported in association with Pediacel, Repevax and Revaxis from launch (27 September 2004) to 31 December 2004 is shown below (Table 1). Distribution data for the vaccines were not available at the time of writing this report and as such, estimated ADR reporting rates (ERRs) have not been calculated.

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

	Pediacel	*Repevax*	*Revaxis*
Total no of reports	42 (12)	99 (16)	51 (16)
Total no of reactions	80 (16)	154 (19)	125 (19)
Total fatal	1	0	0
Total no of doses distributed	N/A	N/A	N/A
ERR for serious reports per 1000 doses	N/A	N/A	N/A

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

The tables on page 2 list the serious ADRs reported from 27 September to 31 December 2004. Overall, the majority of the reactions were in the neurological SOC for all three vaccines. The majority of suspected ADRs associated with Repevax and Revaxis have been signs and symptoms of injection site reactions and vaso-vagal reactions. No new safety signals have been identified.

Given the public interest in the Pediacel around the time of its launch and the fact that the vaccine has Black Triangle status, the number of suspected ADRs received to date is reassuringly low. Most suspected ADRs have been signs and symptoms of recognised reactions and non-serious. The serious ADRs have included one case of blindness and one case of sudden infant death syndrome (12 day onset after

vaccinations). Both cases were co-suspected with MenC vaccine and further clinical details are awaited for both. No new safety signals have been identified.

There was considerable concern among health professionals shortly after launch that the brand names and packaging for Revaxis and Repevax were too similar and cases of the wrong vaccine being given have been reported. A few children were also mistakenly given Repevax instead of Pediacel. MHRA has addressed this issue with the manufacturer and more distinctive packaging has been developed.

Table 2. Pediacel

Suspected ADR	No. reports
Agitation neonatal	1
Blindness	1
Coma	1
Convulsions NOS	2
Cyanosis NOS	3
Gastroenteritis NOS	1
Hyperpyrexia	1
Hypotonia	1
Memory impairment	1
Musculoskeletal stiffness	1
Sudden infant death syndrome	1
Swollen tongue	1
Vasculitic rash	1

Table 3. Repevax

Suspected ADR	No. reports
Blood pressure decreased	1
Cellulitis	3
Contusion	1
Erythema multiforme	1
Febrile convulsion	1
Haematoma NOS	1
Hypotonia	1
Hypotonic-hyporesponsive episode	1
Infection NOS	2
Injection site cellulitis	2
Joint effusion	2
Myositis	1
Syncope	1
Syncope vasovagal	1

Table 4. Revaxis

Suspected ADR	No. reports
Anaphylactic reaction	1
Angioneurotic oedema	1
Bradycardia NOS	1
Cellulitis	2
Chest tightness	1
Dyskinesia	1
Infection NOS	1
Loss of consciousness	2
Lymphadenopathy	2
Musculoskeletal stiffness	1
Syncope	5
Syncope vasovagal	1

2. Wholecell DTP/DTwP+Hib

The total number of suspected ADRs reported in association with wholecell DTP and DTwP+Hib for the last 3 years is shown below (table 5). The total number of ADRs reported decreased compared to 2003 (partly accounted for by the withdrawal of the vaccine in September) but the estimated reporting rate of serious reports (ERR)/1000 doses is similar to 2003.

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

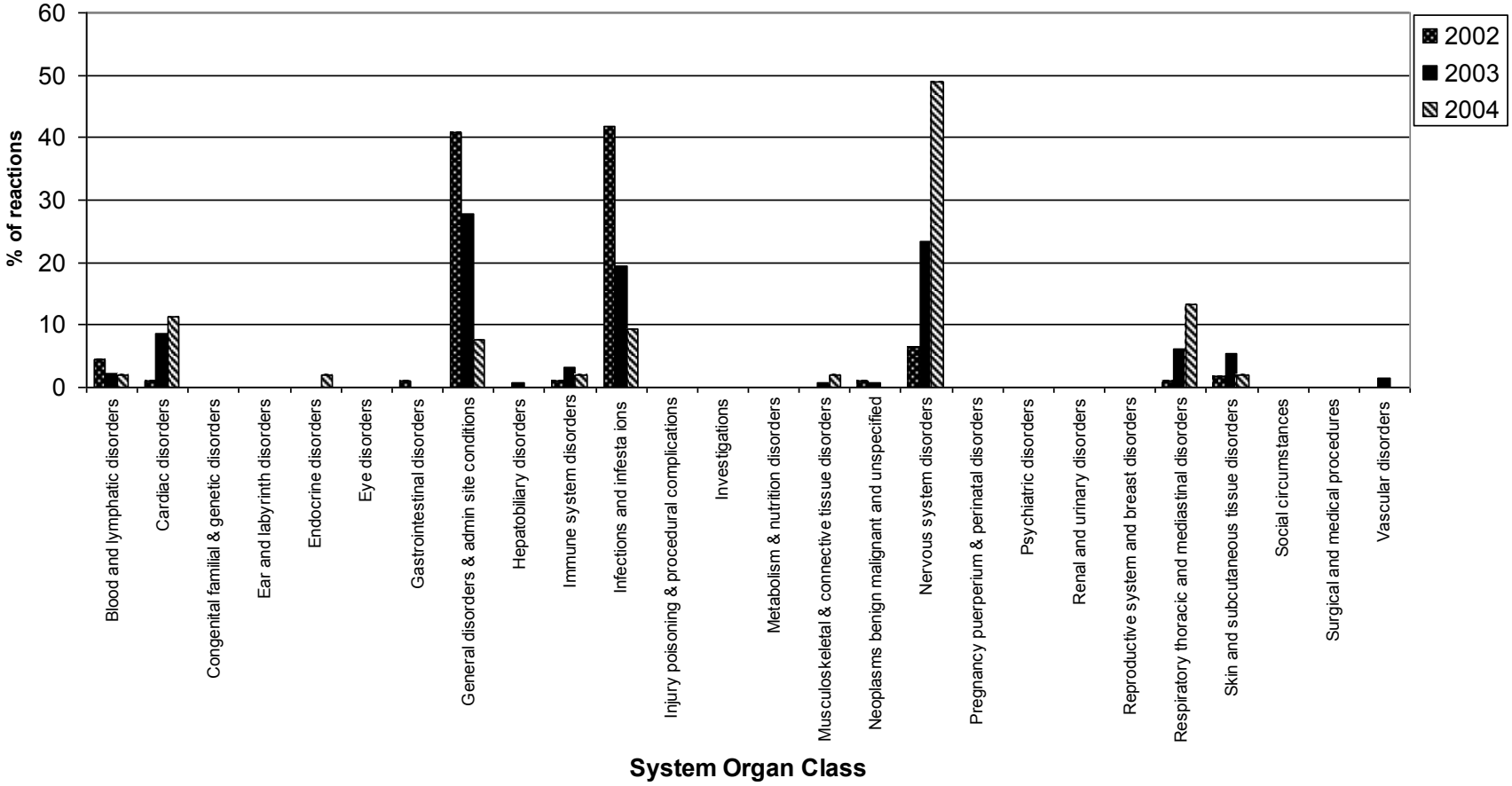
	2002	***2003***	***2004***
Total no of reports	122 (21)	247 (64)	110 (41)
Total no of reactions	222 (22)	487 (81)	192 (52)
Total fatal	0	2	0
Total no of doses distributed	1,608,754	2,136,178	*1,574,638
ERR for serious reports per 1000 doses	0.013	0.029	0.026

ERR = Estimated Reporting Rate

* Distribution data from Jan to Oct 2004

The graph on page 4 (Figure:1) 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 2004 were broadly similar to those reported in the previous two years. Almost 50% of serious ADRs were neurological ADRs and largely consisted of hypotonic hyporesponsive episodes and convulsions. There have been no suspected ADRs with a fatal outcome. No significant new safety issues have been identified.

Figure 1: % of serious reactions associated with Wholecell DTP/DTwP+Hib vaccine



3. Men C

The total number of suspected ADRs reported in association with Meningococcal GP C conjugate vaccine for the last 3 years is shown below (table 6). The total number of reports received in 2004 was lower than 2003 although the serious ERR remained the same.

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

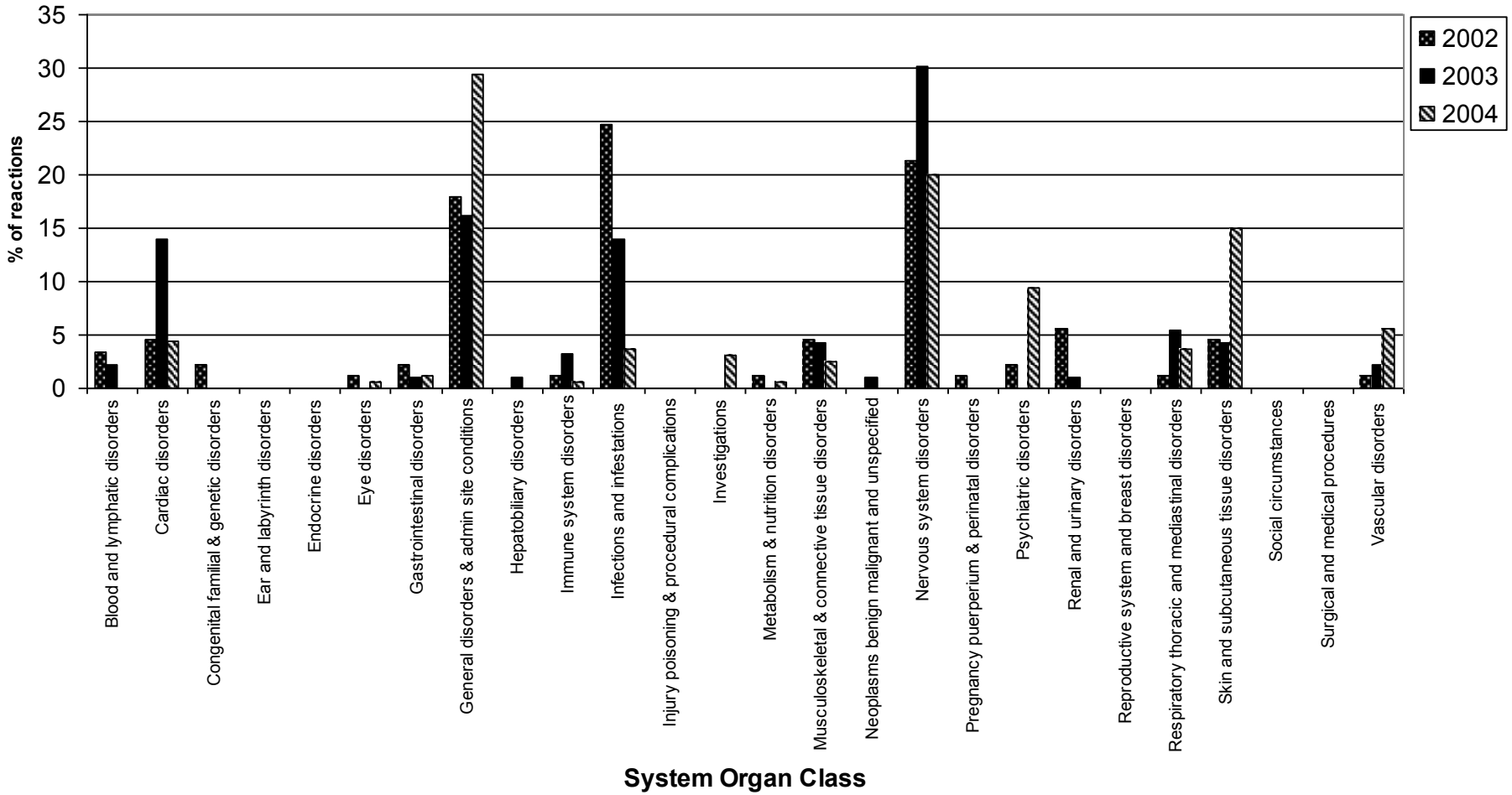
	2002	***2003***	***2004***
Total no of reports	161 (50)	117 (49)	85 (53)
Total no of reactions	297 (60)	259 (67)	160 (68)
Total fatal	1	2	1
Total no of doses distributed	1,901,179	2,206,858	2,265,288
ERR for serious reports per 1000 doses	0.026	0.022	0.023

ERR = Estimated Reporting Rate

Suspected ADR with a fatal outcome: One case of sudden infant death syndrome (co-suspected with Pediacel referred to above.

The following graph (Figure 2) shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. During 2004, a signal of waning efficacy more than 1 year after the last routine dose in infancy was identified by HPA. CSM advised that the SPC for each of the licensed MenC vaccines should be amended to mandate that a booster dose be given after completion of the primary immunisation series in infants. No other significant new safety issues have been identified.

Figure 2: %of serious reactions associated with Meningococcal GP C vaccine



4. Polio vaccine (oral)

The total number of suspected ADRs reported in association with oral polio vaccine for the last 3 years is shown below (table 7). The total number of ADRs reported decreased compared to 2003 however, the serious ERR is similar.

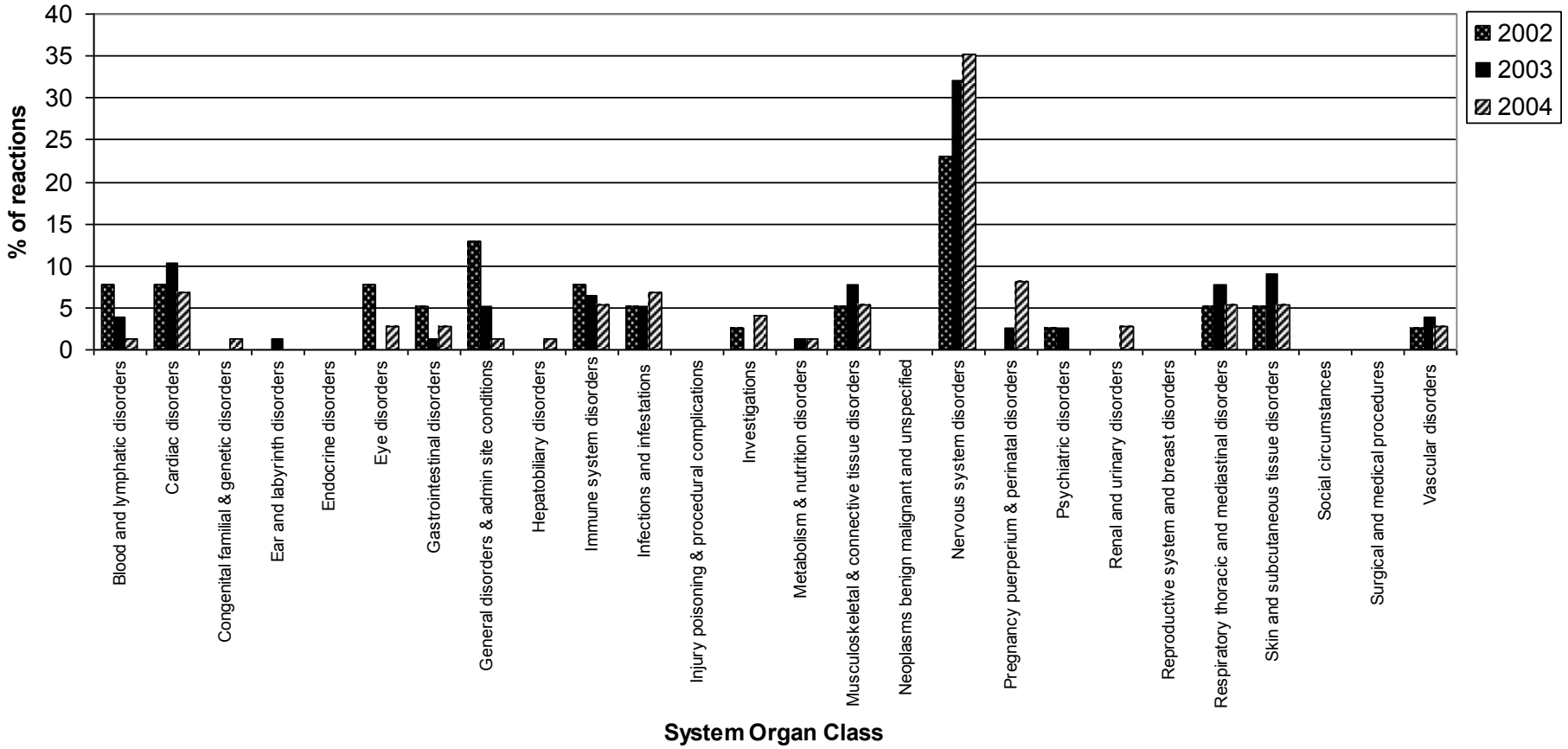
Table 7: Total number of reports and doses distributed (serious reports in brackets)

	2002	***2003***	***2004***
Total no of reports	56 (23)	101 (56)	75 (45)
Total no of reactions	123 (28)	257 (76)	183 (74)
Total fatal	0	2	0
Total no of doses distributed	5,352,520	4,701,710	*3,310,500
ERR for serious reports per 1000 doses	0.004	0.012	0.013

ERR = Estimated Reporting Rate
**Distribution data from Jan to Oct 2004*

The graph on the following page (Figure 3) shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. There have been no reports with fatal outcomes in 2004. No significant new safety issues have been identified.

Figure 3: % of serious reactions associated with oral Poliomyelitis



5. MMR vaccine

The total number of suspected ADRs reported in association with MMR vaccination for the last 3 years is shown below (table 8). Based on the doses distributed, the serious ERR is lower than the preceding two years.

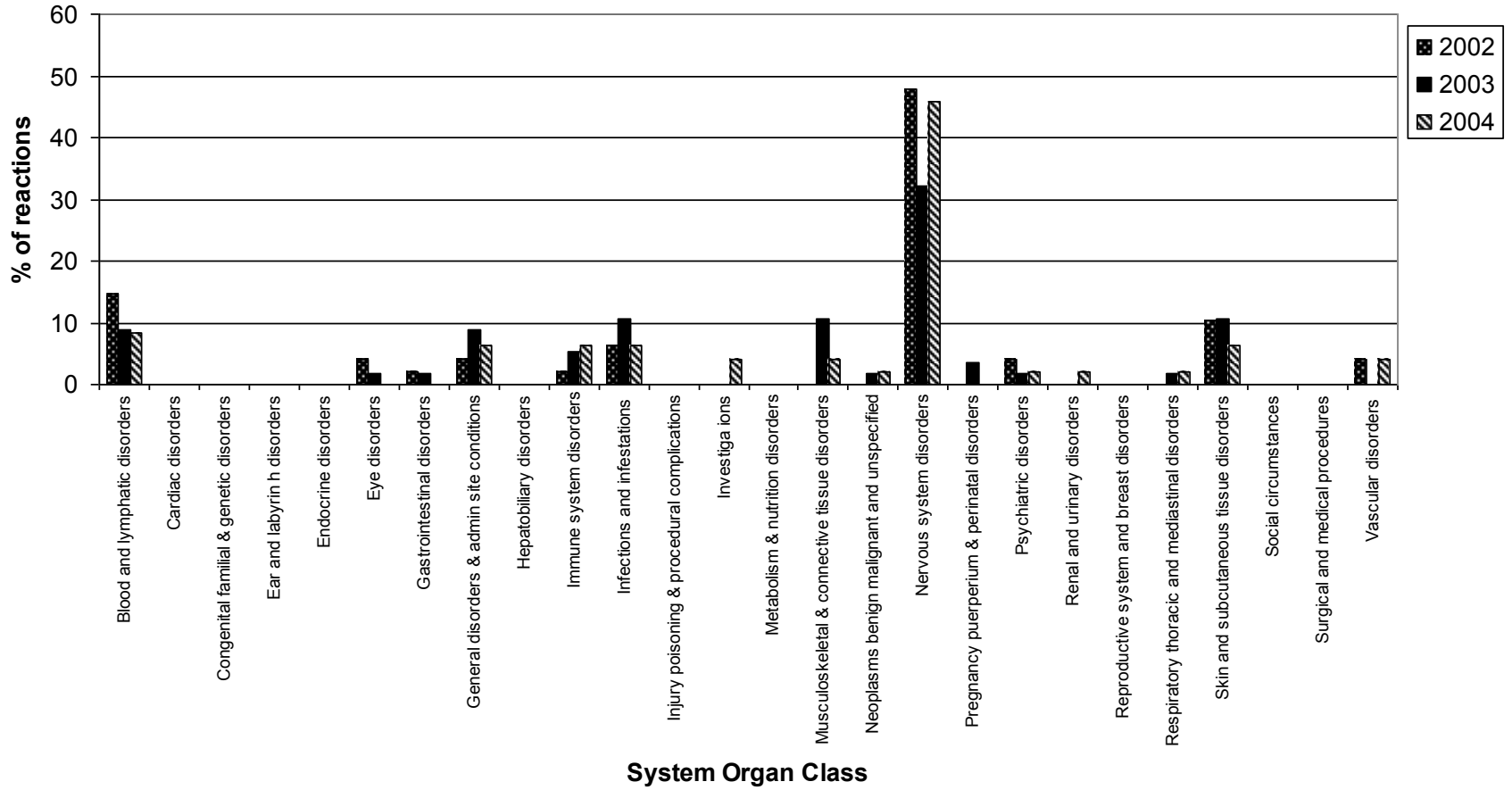
Table 8: Total number of reports and doses distributed (serious reports in brackets)

	2002	*2003*	*2004*
Total no of reports	82 (36)	97 (40)	105 (36)
Total no of reactions	158 (41)	176 (49)	206 (48)
Total fatal	0	1	0
Number of doses distributed	1,354,794	1,391,040	1,928,780
ERR for serious reports per 1000 doses	0.026	0.029	0.018

ERR = Estimated Reporting Rate

The graph on the following page (Figure 4) shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. There have been no reports with fatal outcomes in 2004. Overall, the pattern and type of reactions reported does not appear to have changed and no significant safety issues have been identified.

Figure 4: % of serious reactions associated with MMR vaccine



6. BCG vaccine

The total number of suspected ADRs reported in association with BCG vaccine for the last 3 years is shown below (table 9). The total number of reports received in 2004 decreased markedly compared to 2003although the serious ERR was higher.

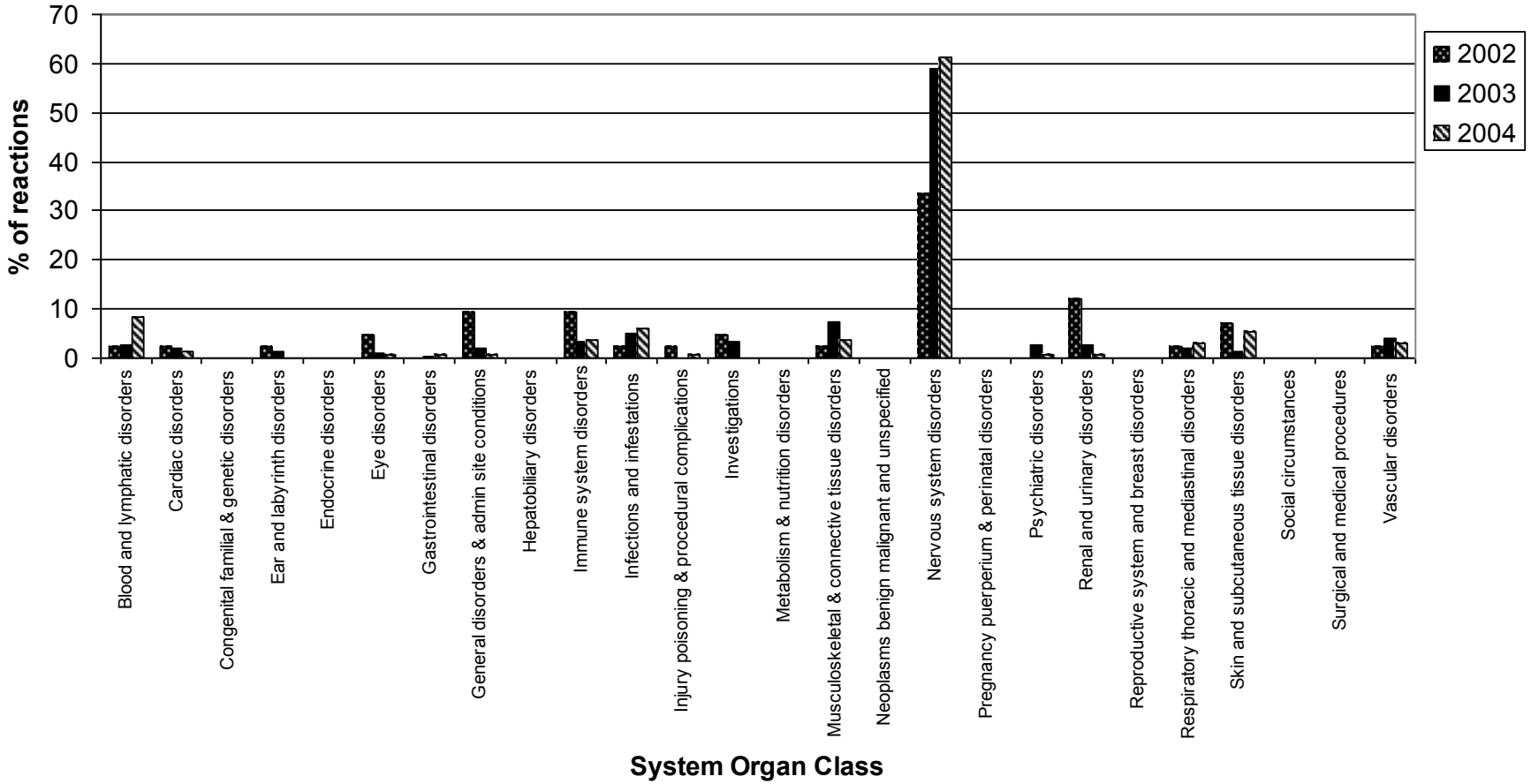
Table 9: Total number of reports and doses distributed (serious reports in brackets)

	2002	***2003***	***2004***
Total no of reports	80 (27)	496 (151)	299 (108)
Total no of reactions	132 (36)	990 (212)	593 (136)
Total fatal	0	0	0
Total no of doses distributed	2,416,130	3,903,900	2,422,800
ERR for serious reports per 1000 doses	0.011	0.038	0.044

ERR = Estimated Reporting Rate

The graph on following page (Figure:5) shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. As in 2003, reporting was broadly split into 2 types of ADR; vaso-vagal reactions and injection site reactions (inc. abscess and associated lymphadenopathy). The majority of serious ADRs were reported in the nervous system SOC and were mainly cases of vaso-vagal reactions. No significant new safety issues have been identified.

Figure 5: % of serious reactions associated with BCG vaccine



7. Hepatitis B vaccine

The total number of suspected ADRs reported in association with single hepatitis B vaccine for the last 3 years is shown below (table 10). The number of reports received in 2004 decreased compared to 2003. However, based on the number of doses distributed the reporting rate of serious reports is lower compared to the previous year.

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

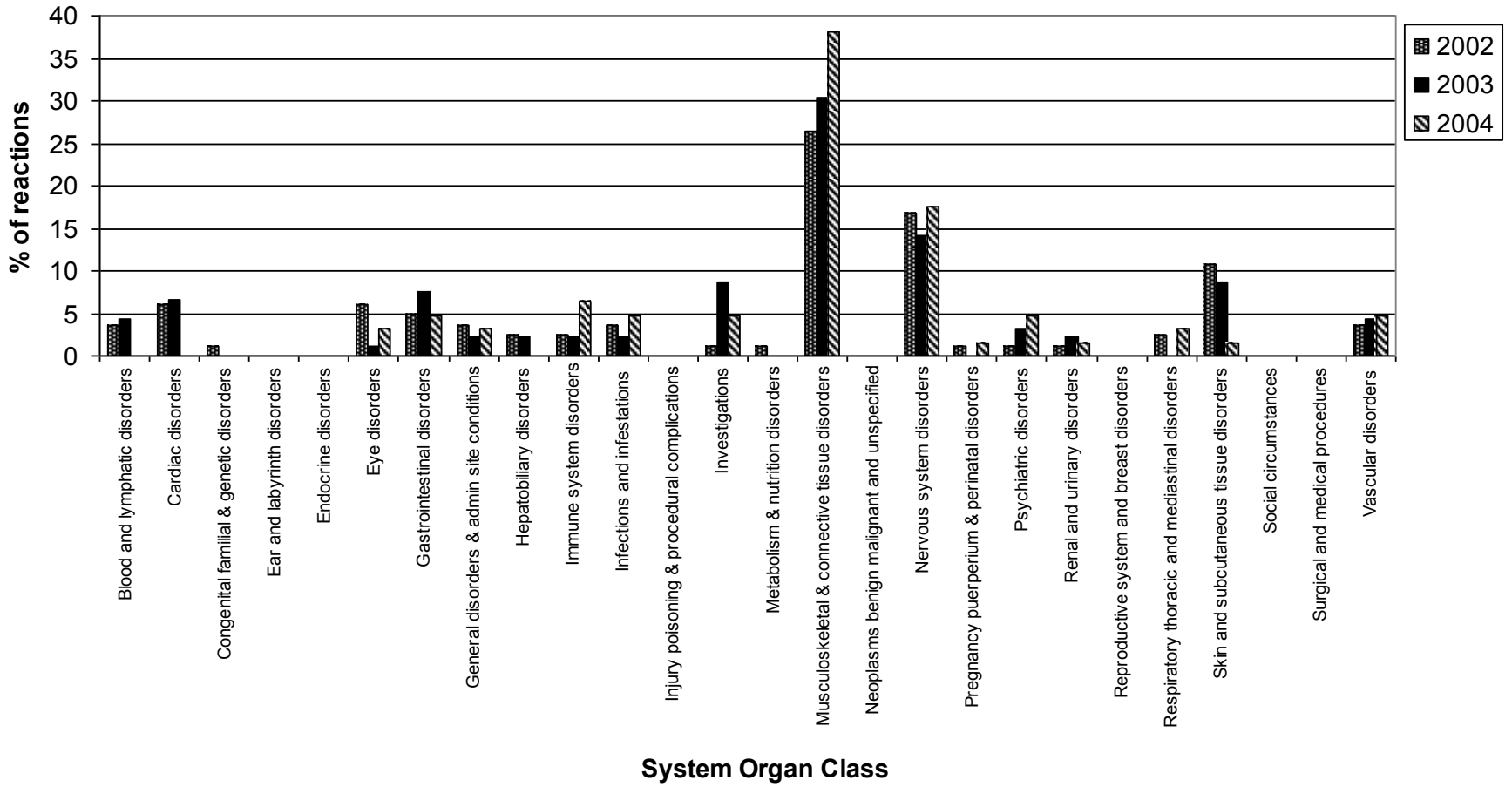
	2002	***2003***	***2004***
Total no of reports	79 (49)	107 (60)	68 (45)
Total no of reactions	205 (74)	311 (88)	187 (60)
Total fatal	0	0	0
Total no of doses sold	1,053,658	1,292,176	1,259,666
ERR for serious reports per 1000 doses	0.046	0.046	0.035

ERR = Estimated Reporting Rate

During 2004, a new study using GPRD identified a significant association between HepB vaccine and multiple sclerosis (3-fold increased risk; Hernan *et al*. *Neurology* 2004; 63: 838-42). CSM considered the findings of this study and advised that due to various outstanding questions/concerns about methodology and confounding/bias, and as 9 previous epidemiological studies found no significant association, the body of available evidence does not provide convincing support for a causal relationship between HepB vaccine and MS.

The following graph (Figure:6) 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.

Figure 6: % of serious reactions associated with Hepatitis B vaccine



8. Influenza vaccine

The total number of suspected ADRs reported in association with influenza vaccine for the last 3 years is shown below (table 11). The distribution data for the vaccine was not available at the time of writing this report and as such, ERRs have not been calculated.

Five suspected ADRs had a fatal outcome: One case each of coronary artery thrombosis, pericardial haemorrhage, sudden death, acute myocardial infarction and pneumocystis carinii pneumonia.

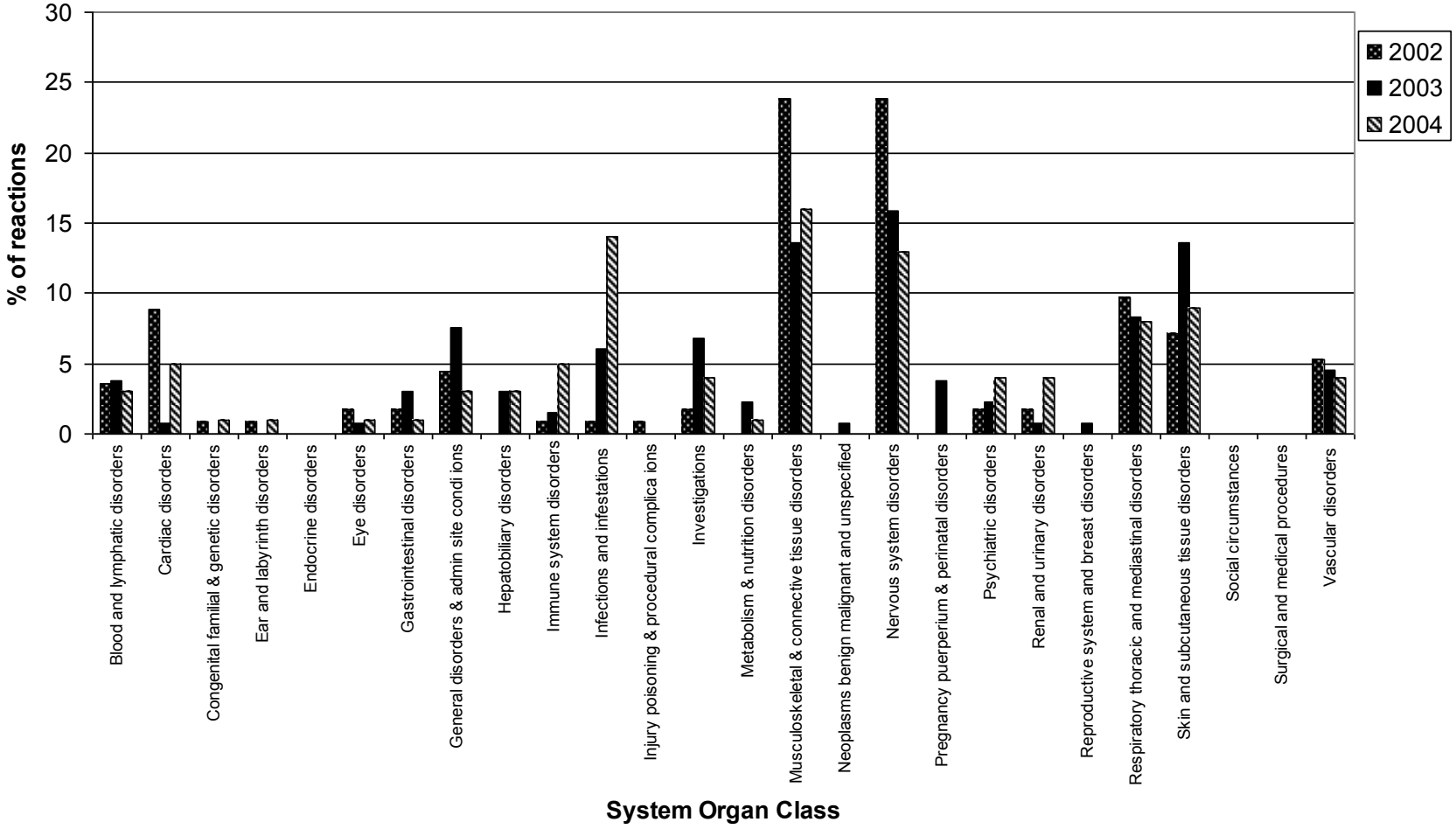
Table 11: Total number of reports and doses distributed (serious reports in brackets)

	2002	***2003***	***2004***
Total no of reports	106 (73)	137 (96)	113 (80)
Total no of reactions	227 (83)	301 (124)	270 (100)
Total fatal	8	4	5
Total no of doses distributed	*N/A*	*N/A*	*N/A*
ERR for serious reports per 1000 doses	*N/A*	*N/A*	*N/A*

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

The graph on page 16 (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.

Figure 7: % of serious reactions associated with Influenza vaccine



9. 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 12).

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

	2002	***2003***	***2004***
Total no of reports	39 (14)	63 (26)	46 (27)
Total no of reactions	84 (14)	121 (32)	100 (36)
Total fatal	1	4	3
Total no of doses distributed	**700,218*	**1,295,961*	**1,655,879*
ERR for serious reports per 1000 doses	*0.019*	*0.020*	*0.016*

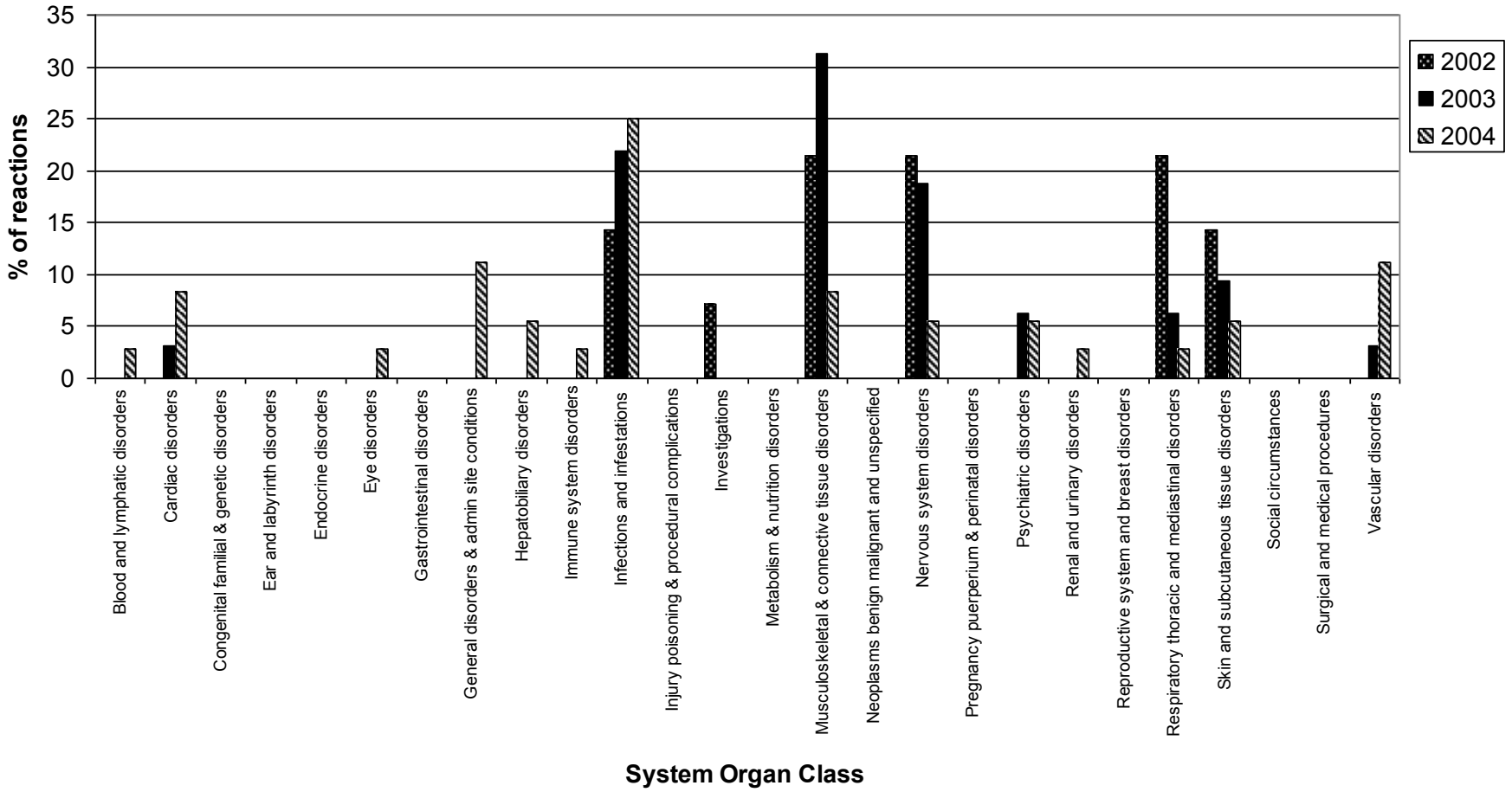
ERR = Estimated Reporting Rate

* Distrubution data from April 2002 – Dec 2002, Jan 2003 – Dec 2003 and Jan 2004 – Nov 2004

The graph on page 18 (Figure:8) shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. Three suspected ADRs had a fatal outcome: One case each of lobar pneumonia, cardiac failure acute and sudden death.

No significant new safety issues have been identified.

Figure 8: % of serious reactions associated with oral Pneumococcal polysaccharide vaccine



10. Pneumococcal conjugate vaccine

The total number of suspected ADRs reported in association with pneumococcal conjugate vaccine for the last 3 years is shown below (table 13). 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 13: Total number of reports (serious reports in brackets)

	2002	***2003***	***2004***
Total no of reports	6 (3)	3 (3)	9 (8)
Total no of reactions	7 (3)	8 (5)	28 (13)
Total fatal	1	0	0
Total no of doses distributed	*N/A*	*N/A*	*N/A*
ERR for serious reports per 1000 doses	*N/A*	*N/A*	*N/A*

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

The table below lists the serious ADRs reported in 2004. No significant new safety issues have been identified.

Table 14.

Suspected ADR	No. reports
Apnoea	1
Apnoeic attack	2
Asthma NOS	1
Bradycardia NOS	3
Convulsions NOS	1
Deafness NOS	1
Gastroenteritis NOS	1
Hypotonia	1
Loss of consciousness	1
Swelling face	1

[redacted]
MHRA-PL
8 February 2005