Paper provided by MHRA for
Joint Committee on Vaccination and Immunisation
June 2010:

VACCINE-ASSOCIATED SUSPECTED ADVERSE REACTIONS REPORTED VIA THE YELLOW CARD SCHEME DURING 2009

June 2010

CONTENTS

Introduction

This paper was prepared by Medicines and Healthcare products Regulatory Agency (MHRA) for the June 2010 Meeting of the Joint Committee of Vaccination and Immunisation (JCVI).

Section 1 of this paper provides an update on UK suspected adverse reactions (ADRs) associated with routine and/or commonly used vaccines reported to the MHRA/CHM via the Yellow Card Scheme during the time period of 1st January 2009 to 31st December 2009.

Precise vaccine exposure data for 2009 were not available at the time of writing this report. For specific vaccines, such as particular routine childhood vaccines, an uptake percentage has been assumed; however it has not been possible to make any assumptions for the remaining vaccines. As a result estimated reporting rates for the former are unreliable and for the latter have not been calculated. As the estimated reporting rates are based on imprecise data and assumptions, no firm conclusions can be drawn on relative rates over time.

Section 2 provides an update on key vaccine safety papers considered by the Commission on Human Medicines (CHM) and/or its Expert Advisory Groups during 2009 and to date.

Prepared: May 2010

[redacted]

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

1. YELLOW CARD DATA

It should be noted that a report of a suspected adverse drug reaction (ADR) to the MHRA/CHM does not necessarily mean that it has been caused by the vaccine. Many factors have to be taken into account in assessing the relationship between a vaccine and suspected reaction such as the possible role of underlying or undiagnosed illness or infection.

Furthermore, the number of reports received should not be used as a basis for estimating the incidence of ADRs due to variable levels of reporting and as the number of individuals immunised is not always known. Percentage uptake has been approximated from NHS immunisation statistics over the year 2008-2009[1].

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

1.1 Routine Childhood Vaccines

1.1.1. Menitorix (MenC/Hib combination)

Menitorix was introduced into the routine childhood schedule in September 2006 as a single dose MenC/Hib booster at around 12 months of age. Although this is a novel combination, prior to introduction there was extensive worldwide experience with the similar monocomponent Hib and MenC vaccines conjugated to tetanus toxoid (e.g. Hiberix and Neisvac-C vaccines).

The total number of suspected ADRs reported in association with Menitorix over the last 3 years is shown below (table 1). On the assumption of 90% uptake (one dose) for an estimated annual birth cohort of 700,000, it estimated that 630,000 children received a single dose of Menitorix during 2009.

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

	2007	2008	2009
Total number of reports	60 (16)	48 (11)	26 (9)
Total number of reactions	114 (17)	105 (20)	67 (11)
Total fatal	0	2	0
Exposure	585,000	585,000	630,000
ERR per 100,000 doses	10.3 (2.7)	8.2 (1.8)	4.1 (1.4)

ERR = Estimated Reporting Rate

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

[1] http://www.ic.nhs.uk/webfiles/publications/immunisationstats0809/NHS_Immunisation_Statistics_England_2008_09_Bulletin.pdf

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

Table 2: Serious ADRs reported for Menitorix (2009)

Serious Suspected ADR		No of Reports
System Organ Class (SOC)	**Preferred Term (PT)**	
Cardiac Disorders	Cyanosis	1
Infections and Infestations	Cellulitis	1
	Infection	1
Injury, Poisoning and Procedural Complications	Wrong Drug Administered	1
	Accidental Overdose	1
Nervous System Disorders	Status Epilepticus	1
	Febrile Convulsion	1
	Hypotonia	1
Psychiatric Disorders	Delirium	1
Respiratory, Thoracic and Mediastinal Disorders	Apnoeic Attack	1
Vascular Disorders	Haematoma	1

Figure 1 shows the serious ADRs reported in each MedDRA System Organ Class (SOC), as a percentage of the total ADRs, for the last three years. The majority of the serious ADRs reported for Menitorix vaccine in 2009 belonged to the 'Nervous System Disorders' SOC, followed by the 'Infections and Infestations' and 'Injury, Poisoning and Procedural Complications' SOCs equally. However, in all cases, numbers of reports were very small.

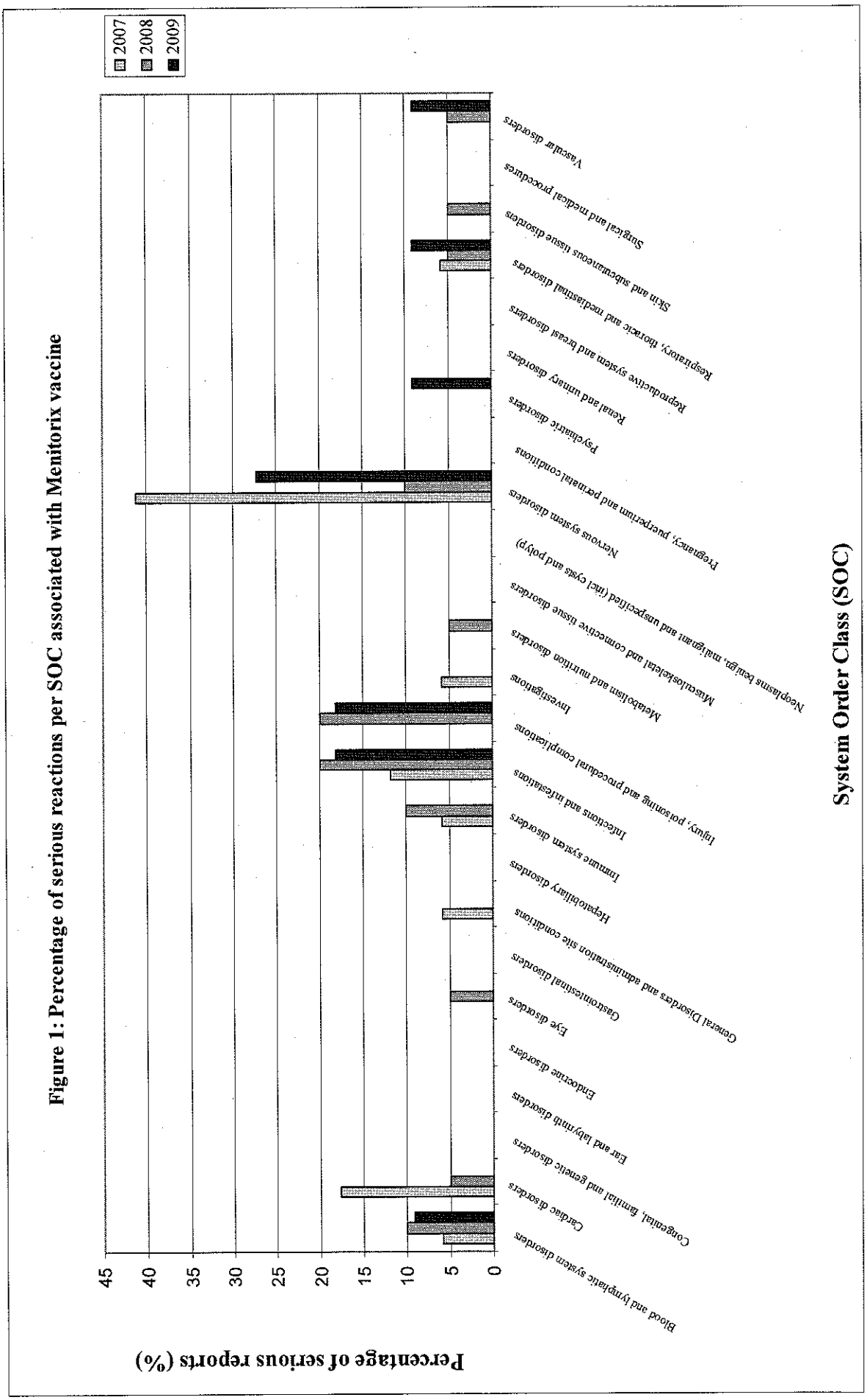
The MHRA is monitoring reports of administration errors which are mainly due to confusion between Menitorix and single constituent Meningitis C vaccine; however the evidence does not suggest that this is due to any packaging issue. This could account for the increased incidence of reports in the 'Injury, Poisoning and Procedural Complications' SOC over the last 2 years.

There were no fatal reactions reported in 2009.

Overall adverse drug reaction reporting numbers remain very small.

Conclusion: No significant new safety issues were identified during 2009.

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



1.1.2. Prevenar (pneumococcal conjugate vaccine)

Prevenar was introduced into the routine childhood schedule in September 2006. It is currently recommended for use at 2 months, 4 months and around 13 months of age. Prior to UK introduction, there was substantial international experience in the safety of pneumococcal conjugate vaccine.

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

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

	2007	2008	2009
Total number of reports	294 (79)	146 (37)	86 (27)
Total number of reactions	679 (107)	325 (44)	218 (39)
Total fatal	2	3	3
Exposure	1,800,000	1,800,000	1,900,000
ERR per 100,000 doses	16.3 (4.4)	8.1 (2.1)	4.5 (1.4)

ERR = Estimated Reporting Rate

On the assumption of 90% uptake for an annual birth cohort of 700,000 (3 doses), it estimated that 1.9m doses of Prevenar were administered during 2009.

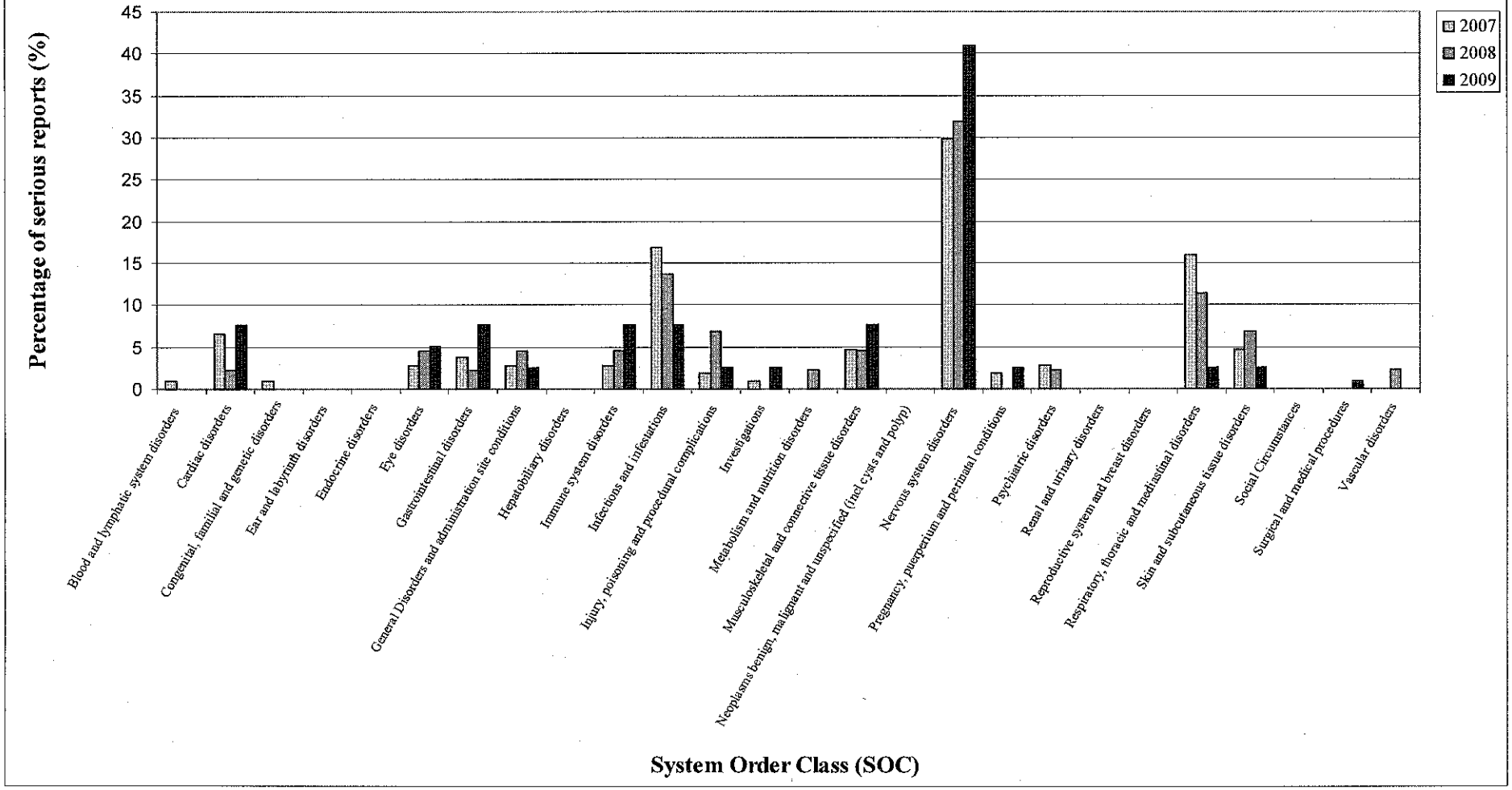
Figure 2 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. As in previous years, the majority of the serious ADRs reported for Prevenar vaccine in 2009 belong to the 'Nervous System Disorders' SOC. There was an increase in the percentage of serious reactions reported in the 'Nervous system disorders' SOC. The most reported serious reaction from this SOC is relating to convulsions' (4 cases - 2 of 'Convulsion', 1 of 'Epilepsy' and 1 of 'Grand Mal Convulsion'), followed by 'Hypotonia' (3 cases), 'Syncope' and 'Loss of Consciousness' (2 cases of each). Seizures (including febrile) are rare recognised adverse reactions to the vaccine.

Three fatal reports were received in 2009; one of cardiac arrest, one of sudden death and one report of anaphylactic reaction. After follow-up with the original reporter, a casual association with these fatal events has not been established.

It is notable that overall reporting rates have reduced over time which possibly reflects familiarity with the vaccine. The black triangle status for this vaccine was removed in June 2008.

Conclusion: No significant new safety issues were identified during 2009.

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



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

DTPa/IPV/Hib vaccine is indicated for primary and booster vaccination against diphtheria, tetanus, pertussis, poliomyelitis and invasive Haemophilus influenzae type b disease from the age of 2 months up to the fourth birthday. It is a 3 dose primary course, administered at 2, 3 and 4 months of age, with a booster given 3 years after completion of the primary course.

The total number of suspected ADRs reported in association with DTPa/IPV/Hib for the last 3 years is shown below (table 4).

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

	2007	2008	2009
Total number of reports	170 (48)	264 (61)	120 (38)
Total number of reactions	405 (66)	589 (87)	313 (63)
Total fatal	1	5	1
Exposure	2,000,000	2,340,000	1,950,000
ERR per 100,000 doses	8.5 (2.4)	11.3 (3.1)	6.2 (1.9)

ERR = Estimated Reporting Rate

The total number of ADRs increased in 2008 compared to 2007. This is partly explained by the increased exposure of the vaccine(s) as a pre-school booster from the end of 2007.

A Haemophilus influenzae type B (Hib) vaccine catch-up campaign was started in early September 2007 and ran until March 2009. The use of Repevax (dTaP/IPV) and Infanrix IPV (DTaP/IPV) as pre-school boosters was replaced with Infanrix IPV Hib (DTaP IPV Hib) vaccine (and possibly Pediacel in a few cases). This accounts for the increased exposure during 2008, and potentially for the decrease in reports in 2009 compared with 2008, after the catch-up campaign ended in the March.

It is estimated that 1.95m doses of DTaP/IPV/Hib were administered during 2009, assuming 93% uptake for an annual birth cohort of 700,000 [3 doses]. However, the true figure is likely to be higher than this due to the Hib catch-up campaign.

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

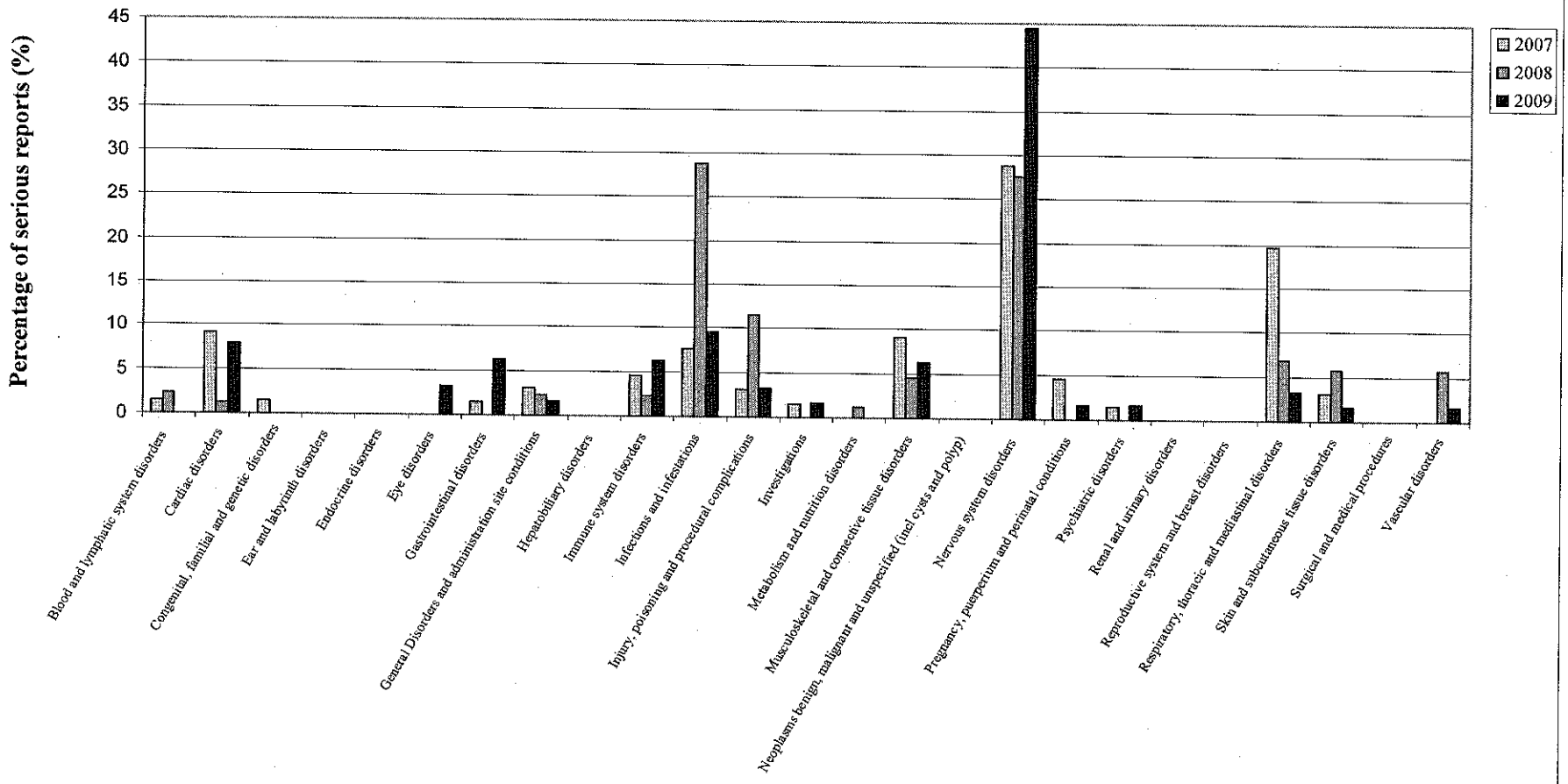
Approximately 45% of serious ADRs were from the 'Nervous System Disorders' SOC and largely consisted of 'Hypotonia' and 'Convulsion' (hypotonic hyporesponsive episodes and convulsions are recognised reactions). This was an increase from 25% of all ADRs last year. There was a marked decrease in the number of serious ADRs in the 'Infections and Infestations' SOC.

There was a decrease in percentage of reactions in the 'Injury, Poisoning and Procedural Complications' SOC; these mostly consisted of vaccine complications or failures. This reflects recovery from the issue in 2008 of administration errors allegedly due to foreign-labelled packs of Infanrix IPV Hib.

One fatal report of cardiac arrest has been reported in association with DTaP/IPV/Hib vaccine in 2009. A casual association with this fatal event has not been established.

Conclusion: No significant new safety issues were identified during 2009.

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



1.1.4. MMR vaccine

MMR vaccine is used for both primary immunisation as a 2-dose schedule at 13 months and at 3 – 5 years, and for revaccination of children over 9 months, adolescents and adults. A new MMR vaccine, M-M-R VaxPro▼ (M-M-R II with recombinant albumin), was introduced in December 2008.

The total number of suspected ADRs reported in association with MMR vaccination for the last 3 years is shown below (table 5).

On the assumption of 86% uptake for an annual birth cohort of 700,000 (2 doses), it estimated that 1,204,000 routine doses of MMR were administered during 2009. However, due to ongoing catch-up initiatives, exposure is likely to be much greater than this.

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

	2007	2008	2009
Total number of reports	100 (51)	123 (65)	145 (70)
Total number of reactions	295 (81)	310 (90)	420 (107)
Total fatal	2	1	3
Exposure	1,105,000	1,105,000	1,204,000
ERR per 100,000 doses	9.0 (4.6)	11.1 (5.9)	12.0 (5.8)

ERR = Estimated Reporting Rate

Figure 4 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. Overall, the pattern and type of reactions has not changed with the most reported serious reactions relating to convulsions (7 cases – 4 of 'Convulsion', 1 'Epilepsy', 1 'Febrile Convulsion' and 1 'Grand Mal Convulsion'), 'Idiopathic Thrombocytopenic Purpura' (6 cases) and 'Cellulitis' (6 cases). Seizures, thrombocytopenia, thrombocytopenic purpura and injection site reactions are listed for the MMR vaccines.

The percentage of serious reactions reported in the 'Nervous System Disorders' SOC has decreased steadily over the last 3 years; however this is still the SOC with the highest percentage of reactions.

The percentage of serious reactions reported in the 'Infections and Infestations' SOC increased slightly to 14% in 2009, compared to 8% in 2008. The most commonly reported reaction in this SOC was 'Cellulitis' (6 cases).

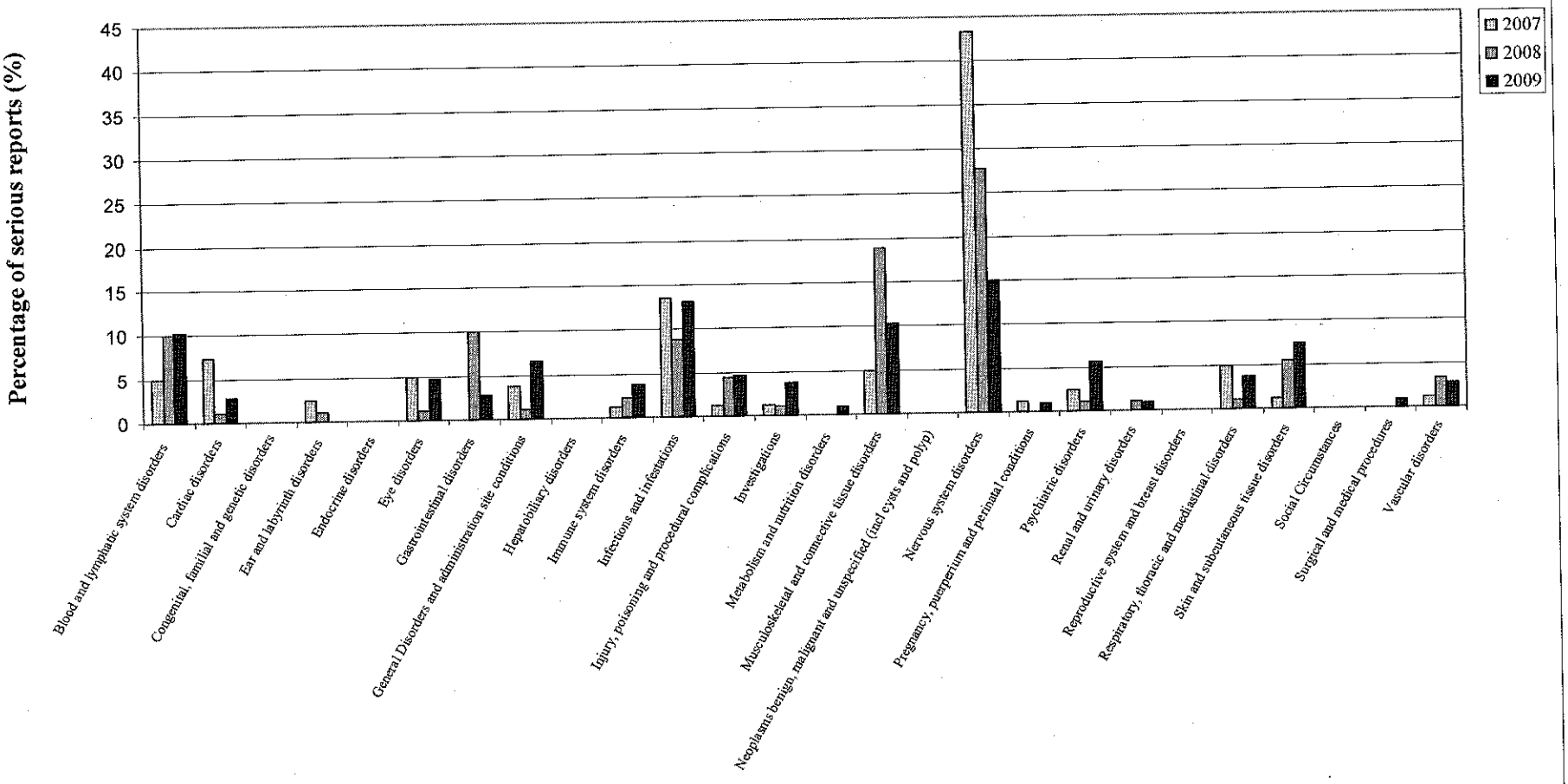
There was also an increase in the percentage of serious reactions in the 'General Disorders and Administration Site Conditions' SOC; the most commonly reported reaction in this SOC was 'Chest Discomfort' (3 cases).

There were three fatal reports reported during 2009; one case of anaphylactic reaction, one case of death and a third of sudden death. These cases were all co-suspect with

pneumococcal conjugate vaccine. A causal association with these fatal events has not been established.

Conclusion: No significant new safety issues were identified during 2009.

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



1.1.5. Meningitis C vaccine

Meningococcal group C conjugate vaccine is recommended for use at 3 and 4 months of age as a primary course (2 dose schedule).

The total number of suspected ADRs reported in association with Meningococcal group C conjugate vaccine for the last 3 years is shown below (table 6).

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

	2007	2008	2009
Total number of reports	65 (18)	54 (16)	45 (13)
Total number of reactions	145 (28)	124 (29)	95 (21)
Total fatal	0	2	0
Exposure	1,170,000	1,170,000	1,290,000
ERR per 100,000 doses	5.6 (1.5)	4.6 (1.4)	3.5 (1.0)

ERR = Estimated Reporting Rate

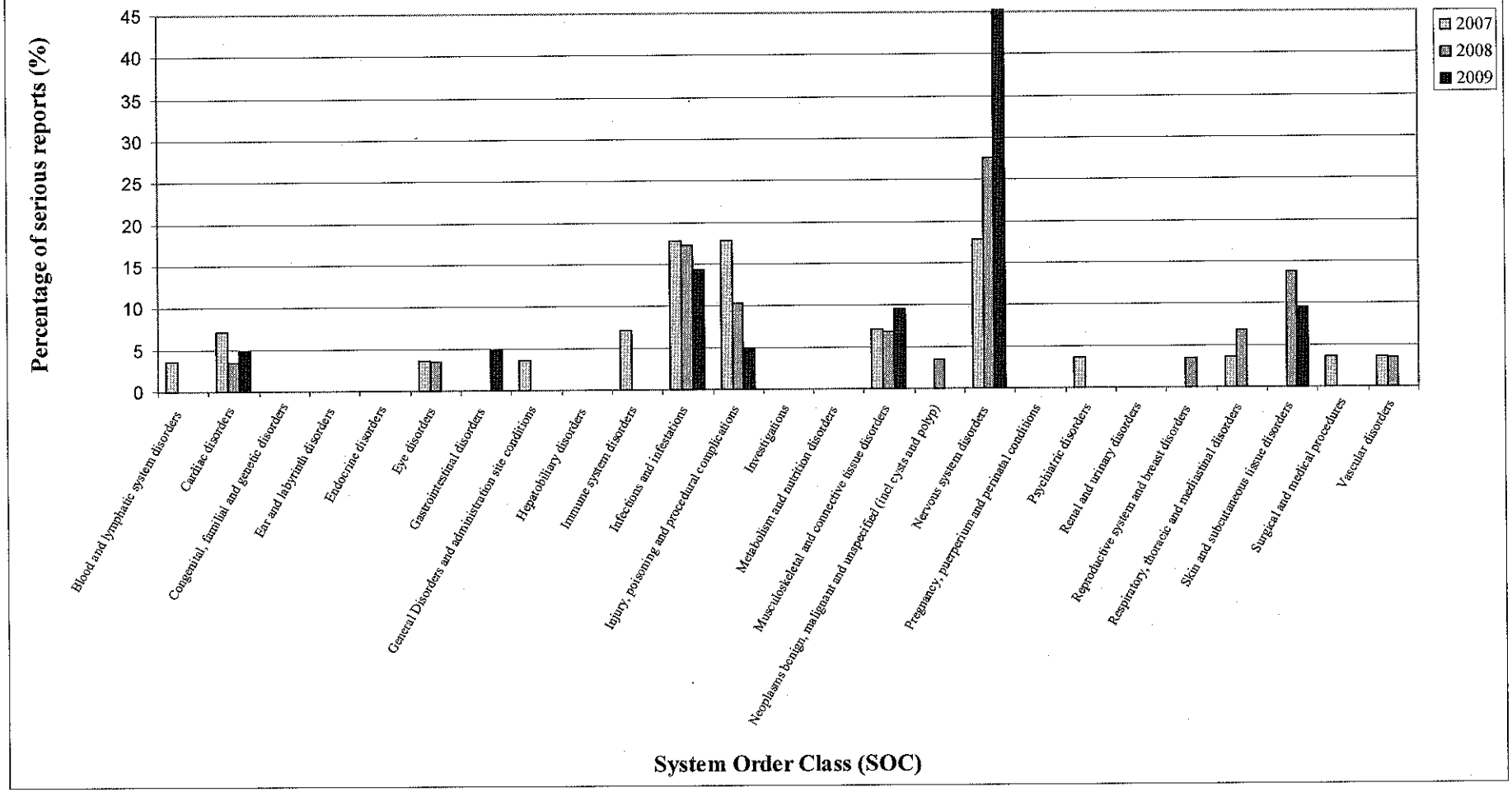
On the assumption of 92% uptake for an annual birth cohort of 700,000 (2 doses), it is estimated that 1.29m doses of Meningitis C conjugate vaccines were administered during 2009.

Figure 5 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last 3 years. The SOC with the largest proportion of serious reactions was the 'Nervous System Disorders' SOC, with the most reported serious reactions in this SOC being 'Hypotonia' (4 cases) and 'Unresponsive to Stimuli' (4 cases). Hypotonia and faints are listed in the Summary of Product Characteristics for the meningitis C vaccine 'Menjugate Kit'.

No fatal events were reported during 2009.

Conclusion: No significant new safety issues were identified during 2009.

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



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

d/DTaP/IPV vaccine is currently used as a booster vaccine in patients between 16 months and 13 years of age, at 3 years after completion of the primary course of vaccination. DTPa/IPV/Hib vaccine superseded this vaccine as a primary course of immunisation in September 2007.

The total number of suspected ADRs reported in association with d/DTaP/IPV vaccine for the last 3 years is shown below (table 7).

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

	2007	2008	2009
Total number of reports	70 (14)	9 (1)	32 (7)
Total number of reactions	159 (15)	20 (1)	78 (16)
Total fatal	0	0	0
Exposure	440,000	n/a	n/a
ERR per 100,000 doses	15.9 (3.2)	n/a	n/a

ERR = Estimated Reporting Rate

The exposure rate for Repevax and Infanrix IPV have not been calculated as these vaccines were not routinely used in 2008 or 2009 due to the Hib catch-up campaign and increased use of the DTPa/IPV/Hib vaccines.

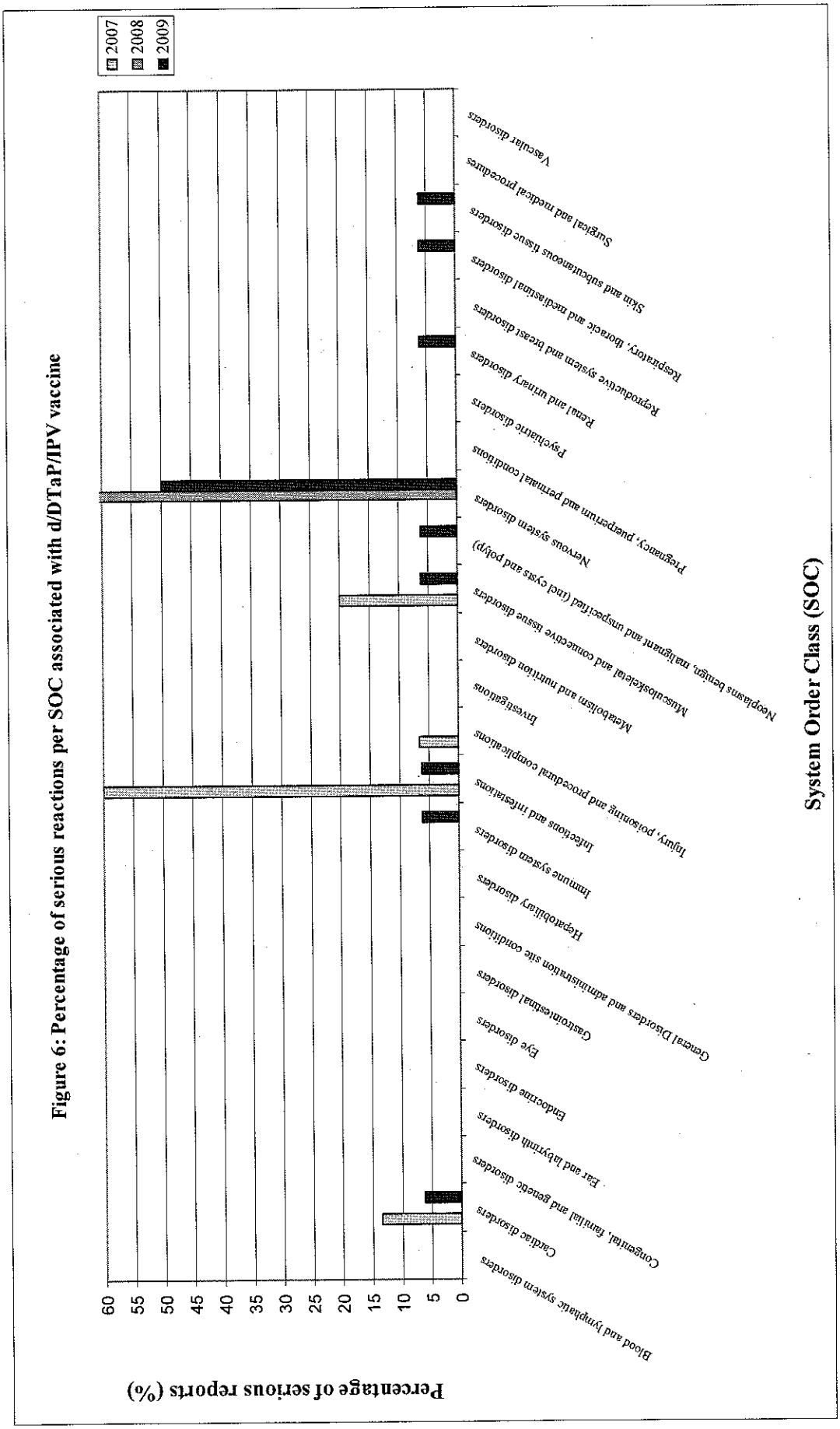
Figure 6 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last 3 years.

The SOC with the largest proportion of serious reactions was the 'Nervous System Disorders' SOC. Reactions reported in this SOC include 'Syncope', 'Loss of Consciousness' and 'Unresponsive to Stimuli' (1 case of each), 'Guillain-Barre Syndrome' (1 case) and 'Myelitis Transverse' (1 case). The SPC for this vaccine lists vasovagal syncope and Guillain-Barre syndrome.

In 2009, only seven cases concerning sixteen serious suspected reactions were reported..
There have been no suspected ADRs with a fatal outcome associated with this vaccine since its launch in 2004.

Conclusion: No significant new safety issues have been identified during 2009.

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



1.1.7. Revaxis (dT/IPV)

Revaxis is a booster vaccine given to young people aged between 13 and 18, as well as being used for adult boosters. The total number of suspected ADRs reported in association with dT/IPV vaccine for the last 3 years is shown below (table 8).

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

	2007	2008	2009
Total number of reports	107 (39)	81 (44)	104 (59)
Total number of reactions	313 (66)	256 (73)	369 (98)
Total fatal	1	2	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.

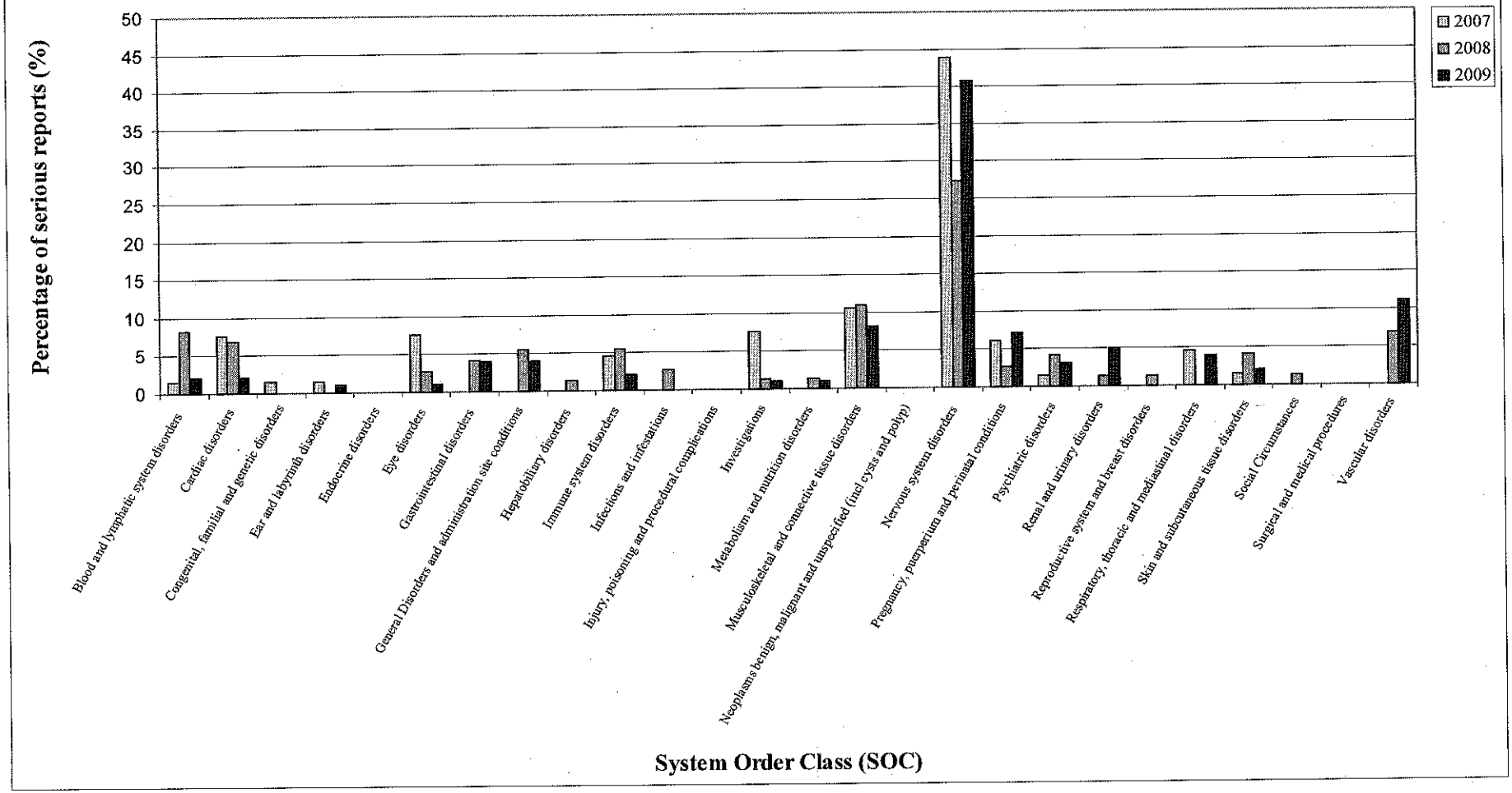
The total number of ADRs reported increased by 25 reports for 2009 compared to 2008. The distribution data for the vaccine during 2009 were not available at the time of writing this report and as such, ERRs have not been calculated.

Figure 7 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. The majority of serious reactions are within the "Nervous System Disorders" SOC with 22 reports of syncope.

There were no fatal reports associated with dT/IPV vaccine.

Conclusion: No significant new safety issues have been identified during 2009.

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



1.2 Other vaccines

1.2.1. Hepatitis B vaccine

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

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

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

	2007	2008	2009
Total number of reports	131 (57)	105 (66)	106 (65)
Total number of reactions	377 (100)	385 (121)	410 (134)
Total fatal	0	2	1
Exposure	n/a	n/a	n/a
ERR per 100,000 doses	n/a	n/a	n/a

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

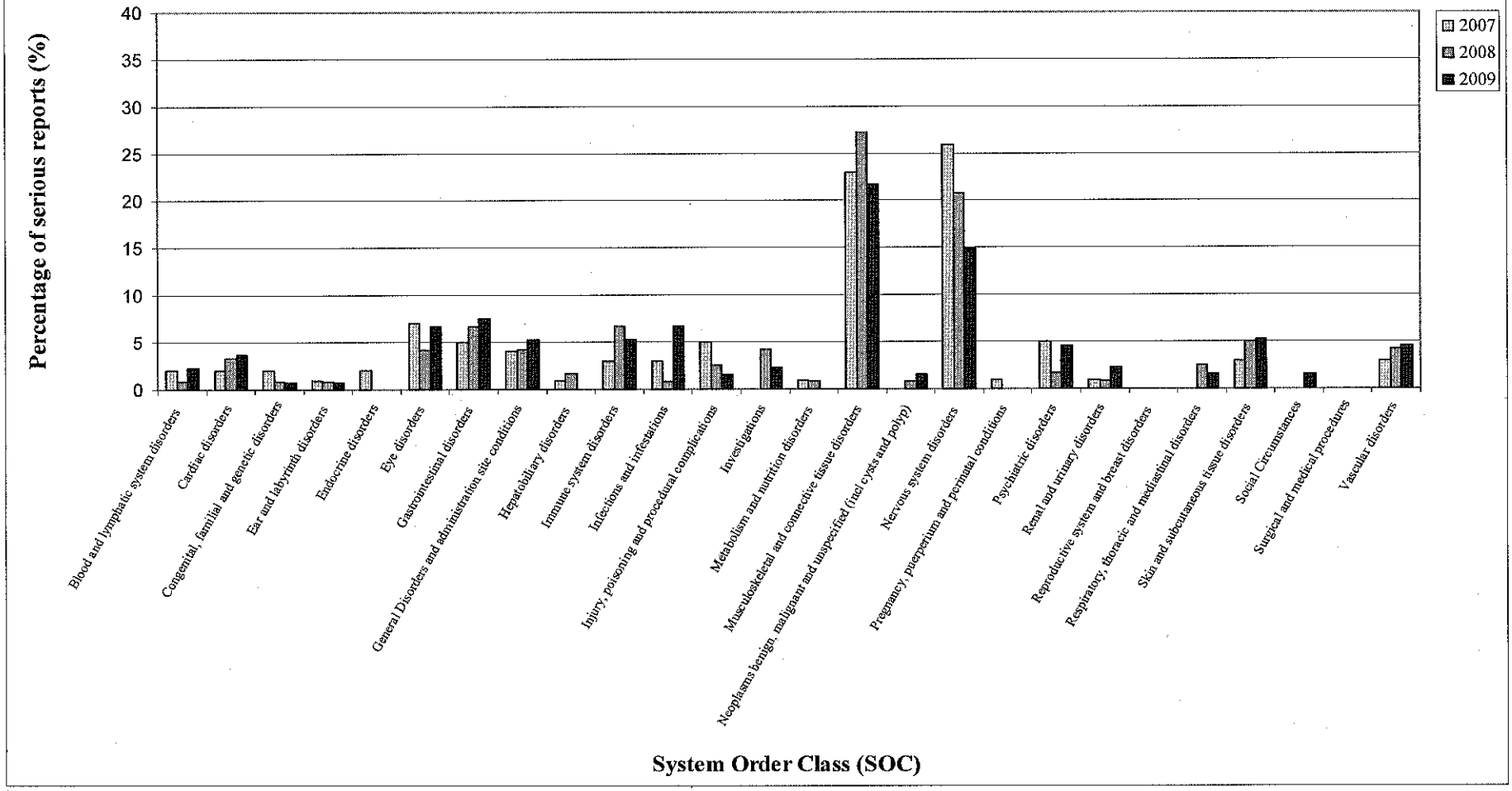
The distribution data for the vaccine during 2009 were not available at the time of writing this report and as such, ERRs have not been calculated.

Figure 8 shows the serious ADRs reported in each SOC, as a percentage of the total serious ADRs, for the last three years. The majority of serious reactions occurred within the 'Musculoskeletal and connective tissue disorders' SOC and the 'Nervous System Disorders' SOC. The most reported serious reaction in each of these two SOCs is 'Arthralgia' (9 cases) and 'Syncope' (4 cases).

There was one fatal report associated with this vaccine in 2009, of viral encephalitis. After follow-up with the original reporter, a casual association with this fatal event has not been established.

Conclusion: No significant new safety issues have been identified during 2009.

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



1.2.2. Influenza vaccine

Influenza vaccine is given to at-risk populations in the community on a yearly basis, including the elderly and those who run an increased risk of associated complications of influenza infection.

The total number of suspected ADRs reported in association with seasonal influenza vaccine for the last 3 years is shown below (table 10). The number of reports received over this period has maintained relatively constant.

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

	2007	2008	2009
Total number of reports	126 (73)	116 (66)	104 (64)
Total number of reactions	353 (110)	322 (108)	337 (131)
Total fatal	5	4	7
Exposure	14,000,000	14,000,000	14,000,000
ERR per 100,000 doses	9.0 (5.2)	8.3 (4.7)	7.4 (4.6)

ERR = Estimated Reporting Rate

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

Figure 9 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. The majority of serious reactions occurred within the 'Musculoskeletal and Connective Tissue Disorders' SOC and the 'Nervous System Disorders' SOC. The most reported serious reactions in the 'Musculoskeletal and Connective Tissue Disorders' SOC were 'Myalgia' (4 cases), 'Arthralgia' (2 cases) and 'Joint Swelling' (2 cases), and in the 'Nervous System Disorders' SOC was 'Guillain-Barre Syndrome' (6 cases). All these reactions are listed in the SPCs for the influenza vaccines.

There was an increase in serious reactions reported in the 'Renal and Urinary Disorders' SOC; the most reported reaction in this SOC was renal failure (2 cases of 'Renal Failure' and 2 of 'Renal Failure Acute'). Renal failure is not listed for influenza vaccine, however 'vasculitis associated in very rare cases with transient renal involvement' is stated in section [4.8] of the SPC. Furthermore, three of these cases are confounded by co-suspect drugs or medical history, and the final case does not contain enough evidence to show a causal association between the vaccine and the reaction.

There were seven suspected ADRs with a fatal outcome in 2009. There were two cases of 'Guillan-Barre Syndrome'; however the available epidemiological evidence does not support a causal association between the current seasonal flu vaccines and GBS. There were two fatal cases of 'Pneumonia Aspiration', one case of 'Encephalitis', one case of 'Myocardial Ischaemia' and one 'unexplained death'.

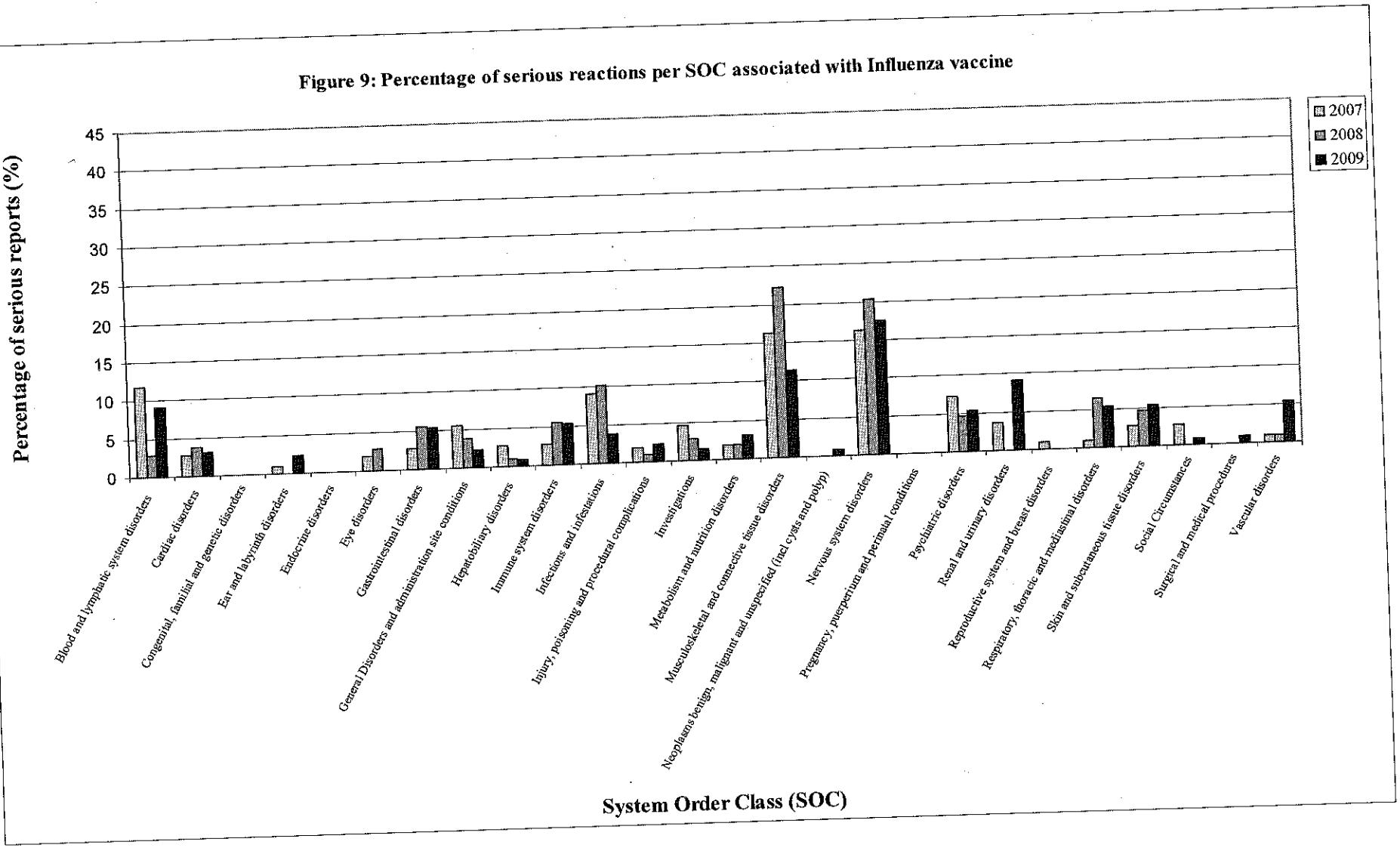
In view of the patient population and in the context of the numbers of doses administered, this does not give rise to concern.

Conclusion: No significant new safety issues have been identified during 2009.

Over the pandemic, the MHRA had in place a separate proactive pharmacovigilance programme to monitor the safety of the new pandemic influenza vaccines, Pandemrix and Celvapan, as they were used in the UK.

It is approximated that over 5 million individuals were vaccinated over the 2009-2010 flu season. The final public summary of all UK reports of suspected adverse reactions to the vaccines is available in annexe 3.

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



1.2.3. Pneumococcal polysaccharide vaccine

Pneumococcal polysaccharide vaccine is recommended for individuals 2 years or older in whom there is an increased risk of complications arising from pneumococcal disease, including over 65s.

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

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

	2007	2008	2009
Total number of reports	93 (41)	88 (26)	40 (12)
Total number of reactions	298 (58)	257 (50)	111 (18)
Total fatal	0	3	0
Exposure	n/a	n/a	n/a
ERR per 100,000 doses	n/a	n/a	n/a

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

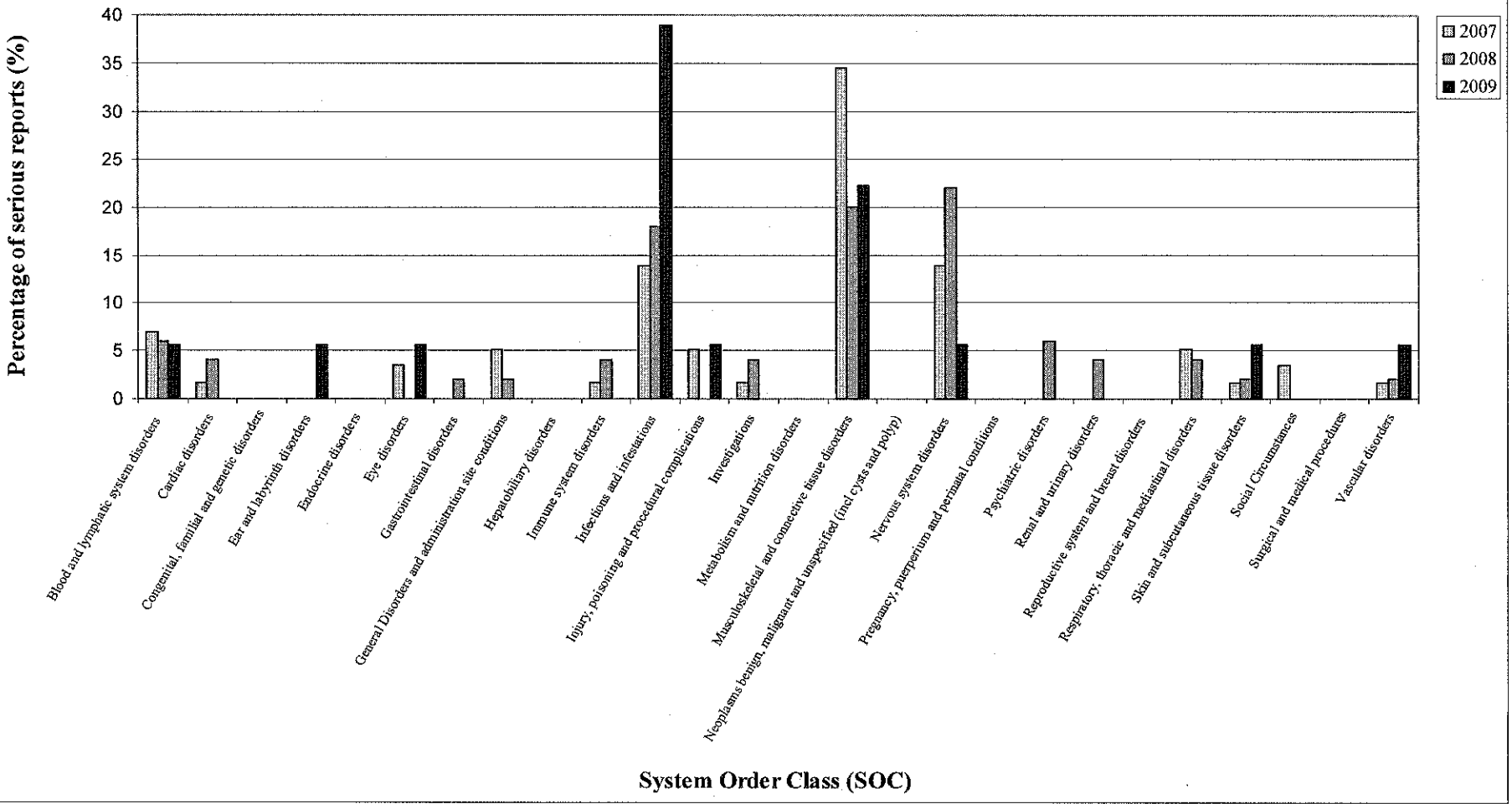
The distribution data for the vaccine during 2009 were not available at the time of writing this report and as such, ERRs have not been calculated.

Figure 10 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. The majority of serious reactions occurred within the 'Infections and Infestations' SOC and the 'Musculoskeletal and Connective Tissue Disorders' SOC. The most reported serious reaction in each of these two SOCs is 'Cellulitis' (3 cases of cellulitis and 1 of injection site cellulitis) and 'Myalgia' (2 cases), which are recognised reactions.

There were no reports of fatal events associated with pneumococcal polysaccharide vaccine in 2009.

Conclusion: No significant new safety issues have been identified during 2009.

Figure 10: Percentage of serious reactions per SOC associated with Pneumococcal Polysaccharide vaccine



1.2.4. BCG vaccine

BCG vaccine is not given as part of the routine childhood vaccination schedule unless a child is thought to have an increased risk of coming in to contact with tuberculosis. It is also recommended for individuals who have increased risk of developing TB, for example healthcare workers or those coming in to close contact with infected individuals.

The total number of suspected ADRs reported in association with BCG vaccine for the last 3 years is shown below (table 12).

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

	2007	2008	2009
Total number of reports	40 (22)	32 (13)	23 (12)
Total number of reactions	63 (24)	49 (16)	39 (17)
Total fatal	0	0	0
Exposure	n/a	n/a	n/a
ERR per 100,000 doses	n/a	n/a	n/a

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

The distribution data for the vaccine during 2009 were not available at the time of writing this report and as such, ERRs have not been calculated.

Figure 11 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years. The majority of serious reactions occurred within the 'Blood and Lymphatic System Disorders' SOC, the 'General Disorders and Administration Site Conditions' SOC and the 'Musculoskeletal and Connective Tissue Disorders' SOC.

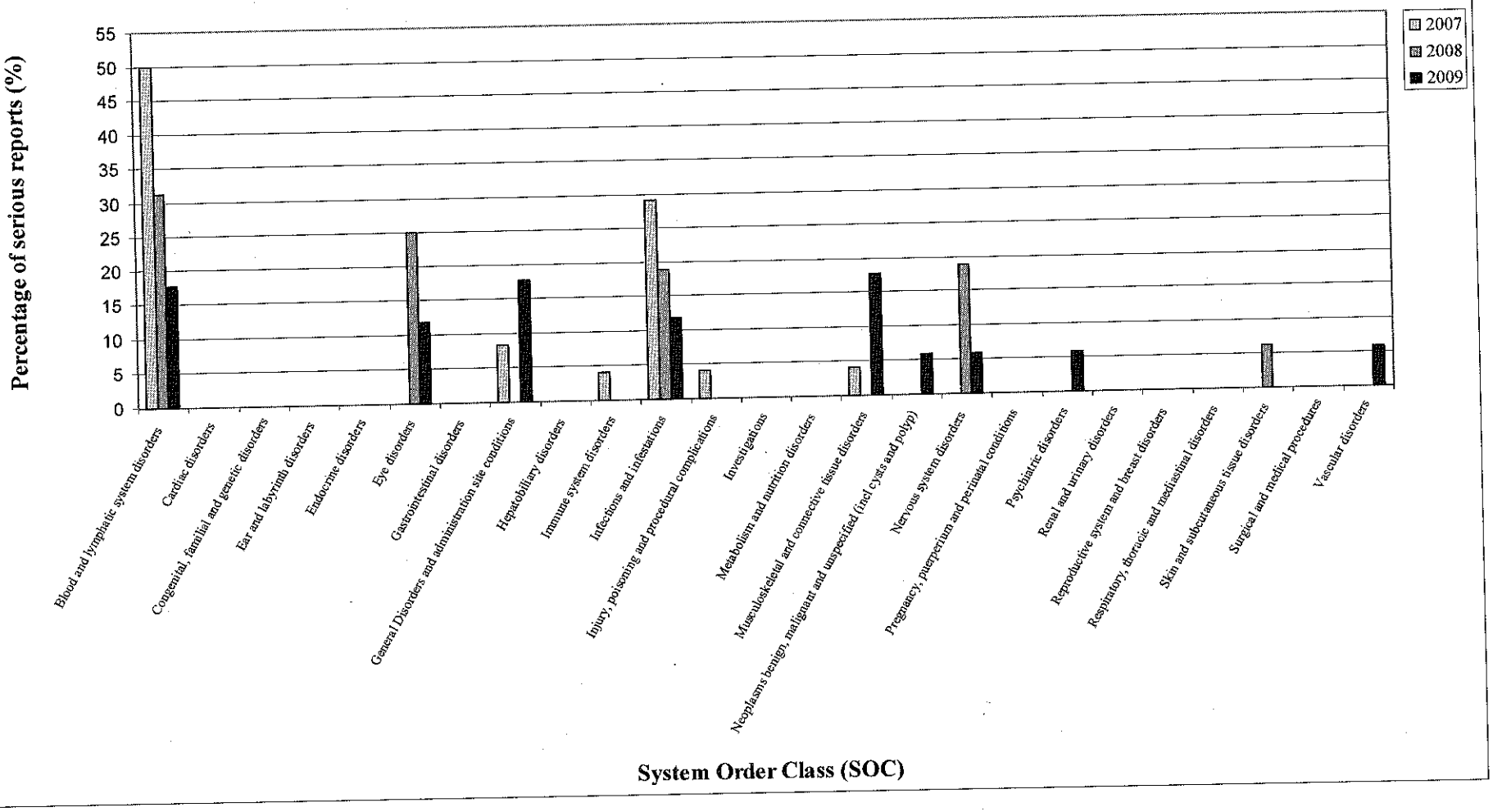
There were only 3 reactions in the 'Blood and Lymphatic System Disorders' SOC; these were 'Lymphadenitis' (2 cases) and one case of 'Lymphadenopathy' (both of which are recognised reactions).

There was one case of 'Arthralgia', one case of 'Joint Stiffness' and one case of 'Joint Swelling' reported in the 'Musculoskeletal and Connective Tissue Disorders' SOC.

No fatal events were reported in association with BCG vaccine in 2009.

Conclusion: No significant new safety issues have been identified during 2009.

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



1.2.5. 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 13).

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

	2007	2008	2009
Total number of reports	23 (15)	19 (12)	13 (6)
Total number of reactions	58 (23)	49 (24)	38 (10)
Total fatal	0	0	0
Exposure	n/a	n/a	n/a
ERR per 100,000 doses	n/a	n/a	n/a

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

The distribution data for the vaccine during 2009 were not available at the time of writing this report and as such, ERRs have not been calculated.

The table below (Table 14) lists the serious ADRs reported in 2009 (note – one Yellow Card may contain more than one serious ADR). Seriousness is determined by regulatory criteria.

Table 14: Serious reactions reported for Varicella Zoster Virus

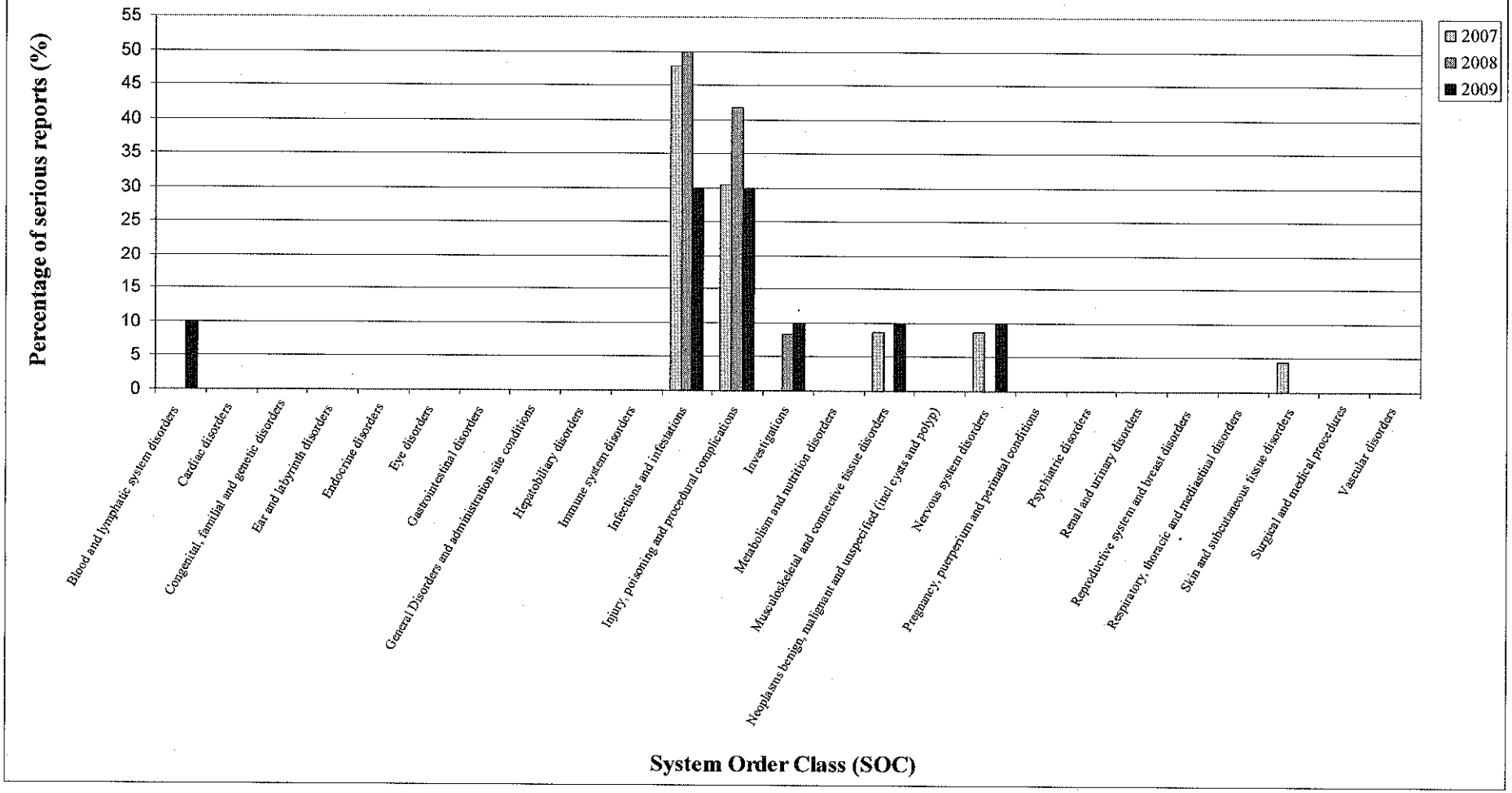
Reaction (PT)	Number of Reports
VACCINATION FAILURE	3
VARICELLA	2
SPLENOMEGALY	1
POST VIRAL FATIGUE SYNDROME	1
LIVER FUNCTION TEST ABNORMAL	1
MYALGIA	1
FACIAL PALSY	1

The majority of serious reactions occurred within the 'Injury, poisoning and procedural complications' SOC and the 'Infections and infestations' SOC. These were mainly vaccination failure (3 cases) and varicella (2 cases). Figure 12 shows the serious ADRs reported in each SOC, as a percentage of the total ADRs, for the last three years.

In relation to vaccine failures, the Summaries of Product Characteristics (SPCs) for Varivax and Varilrix were updated in 2008 to include a two-dose schedule in order to provide long-term protection.

Conclusion: No significant new safety issues have been identified during 2009.

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



2. SECTION 2: ISSUES CONSIDERED BY THE COMMISSION ON HUMAN MEDICINES (CHM) AND/OR ITS EXPERT ADVISORY GROUPS DURING 2009 AND TO DATE

2.1 Update on Rotateq vaccine and Intussusception and Kawasaki's disease

RotaTeq and Rotarix are both authorised within the EU. The UK is rapporteur for RotaTeq and therefore directly responsible for monitoring its ongoing safety; Belgium is the rapporteur for Rotarix.

Because of previous experience with Rotashield, pre-licensing studies were designed to assess any increased risk of intussusception. Based on these studies there remains no confirmed evidence of an increased risk of intussusception for either vaccine.

Since the approval of these vaccines in Europe, Kawasaki Disease has also been identified as a potential risk in association with RotaTeq.

The final results of a large US post-marketing surveillance study has found no evidence for an increased risk of either intussusception or Kawasaki Disease risk with administration of RotaTeq. Product information is being updated accordingly.

2.2 Human Papillomavirus (HPV) vaccine – Safety Experience with the National HPV Immunisation Programme

Since the start of the national HPV programme, at least 4 million doses of Cervarix have been administered. As of 12th May, MHRA had received 3,933 Yellow Cards, including 8,798 adverse-reaction terms. The majority of suspected adverse reactions related to signs and symptoms of either recognised/known adverse reactions that are listed in the product information or 'psychogenic events'.

With every major vaccine programme where many individuals are immunised in a short period of time, it is inevitable that some serious medical conditions will occur shortly after immunisation and be linked with the vaccine, regardless of causality. Thus, reports may be true side-effects or they may have been caused by coincidental medical conditions resulting from underlying or undiagnosed illness and, as such, would have occurred even in the absence of vaccination.

The MHRA has in place a proactive pharmacovigilance strategy to monitor the safety of Cervarix vaccine as it is used in the UK. Part of this includes comparing background (before the vaccine was introduced) age and sex-specific incidence rates of a wide range of medical conditions (those which may naturally occur in adolescent females and be temporally associated with vaccination) with rates reported via the Yellow Card Scheme.

The most recent Safety Adverse Reaction Analysis reports can be found in Annexes 1 and 2.

ANNEXE 1

'Cervarix' Suspected Adverse Reaction Analysis

Safeguarding public health

Suspected Adverse Reaction Analysis

CERVARIX Human papillomavirus (HPV) vaccine

13 May 2010

This report summarises the adverse reactions suspected to have been caused by Cervarix human papillomavirus (HPV) vaccine in the UK. This includes reports received between 14 April 2008 and 12 May 2010. These reports have been voluntarily submitted to the MHRA by healthcare professionals and members of the public via the Yellow Card Scheme (visit www.yellowcard.gov.uk) and by the manufacturers of the vaccine as part of their legal requirements.

It is essential to bear in mind that reports to the MHRA relate only to adverse medical events which the reporter considered could have been caused by the vaccine (i.e. if there was merely a **suspicion** of causality). Therefore, cases may be true side-effects or they may have been purely coincidental events due to underlying or undiagnosed illness that would have occurred anyway in the absence of vaccination. Events may also have been psychogenic[1] in origin. This report therefore cannot be considered to represent a list of known side-effects of the vaccine. These data also cannot be used to determine the frequency, or incidence, of known side-effects because they are often under-reported. The known side-effects, and their frequencies (based on clinical trial data), are available in the product information (see http://emc.medicines.org.uk/).

The reactions in this report have been broken down into 5 categories based on scientific assessment of individual cases by MHRA assessors: injection-site reactions; allergic reactions; 'psychogenic' events; other recognised reactions; and 'suspected adverse reactions not currently recognised' (reactions in this latter category are divided into the high-level classification of System Organ Class)[2]. The same event term may appear in more than one category (e.g. 'rash' may be associated with injection site, allergic or unrecognised suspected reactions and 'psychogenic' events). However, an event from a single report will appear in only one category.

A single report may contain more than one reaction, more than one sign or symptom of a single reaction or different reactions in more than one of the above categories. Therefore the total number of listed reactions is greater than the total number of reports and total reports in each of the 5 tables should not be added together.

Headline summary:

The vast majority of suspected adverse reactions reported to MHRA in association with Cervarix vaccine continue to be related to either the signs and symptoms of recognised side effects listed in the product information or to the injection process and not the vaccine itself (i.e. 'psychogenic' in nature such as faints).

For the isolated cases of other medical conditions reported, the available evidence does not suggest that the vaccine caused the condition and these may have been coincidental events.

Following administration of more than 3.5 million doses across the UK since last September, the balance of risks and benefits of Cervarix remains positive.

[1] For this analysis, defined as non-allergic events which occurred within minutes of, or soon after, vaccination and were most likely a psychogenic response to, or anticipation of, the injection. These are not side effects to the vaccine as such and can occur with any needle injection procedure.
[2] Using MedDRA terminology

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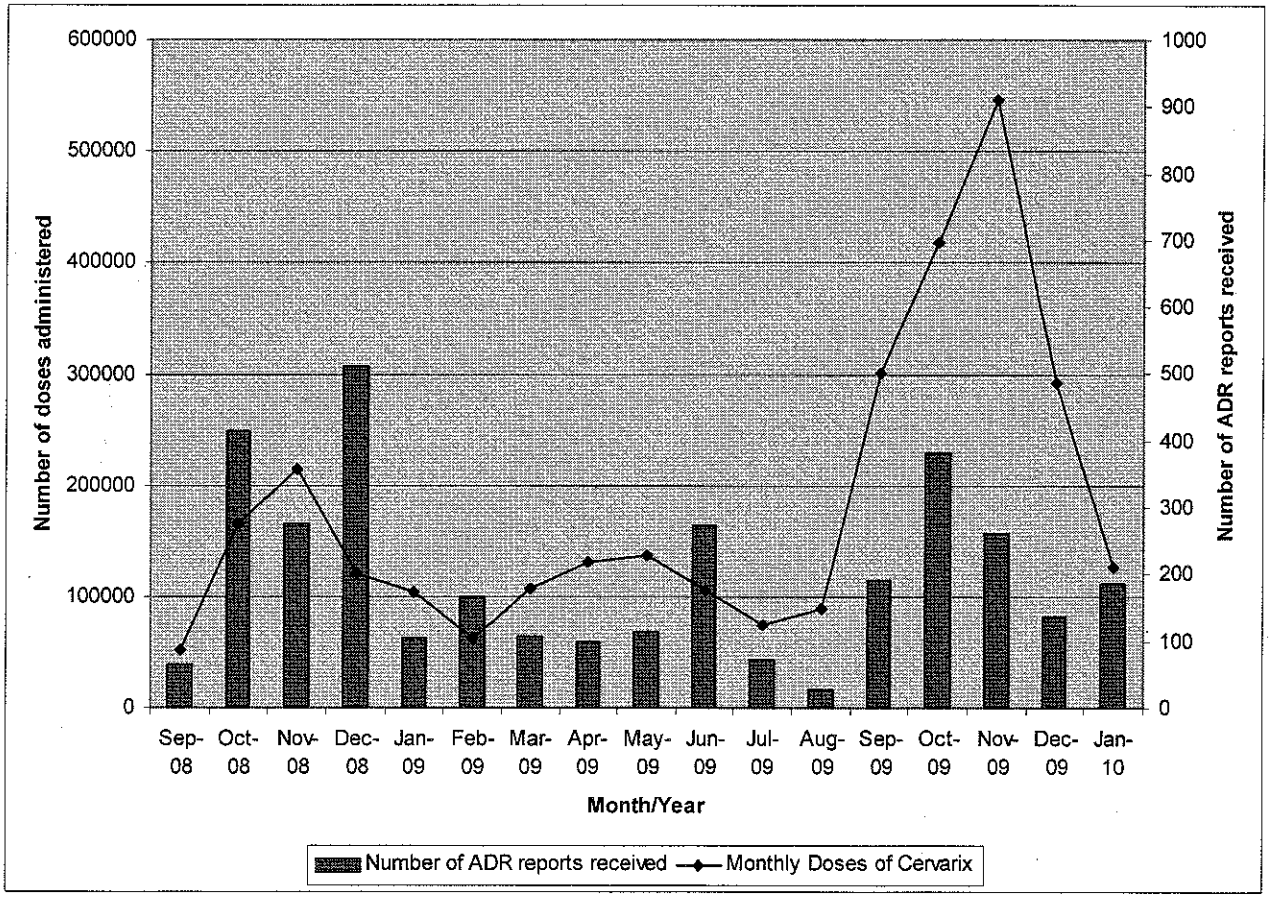
SUMMARY OF UK SAFETY EXPERIENCE

Total number of reports received: 3,933
Total number of suspected reactions: 8,798
Estimated number of doses administered across the UK: at least 3.5 million doses[3]

Graph: Number of suspected ADR reports received relative to doses administered per month



As can be seen from the above graph, peaks in the number of suspected ADR reports received broadly correlate with the timing of the recommended immunisation schedule (i.e. 0, 1-2 months and 6 months from Sep/Oct). Vaccine exposure in the 2nd year is increased due to immunisation of the additional catch-up groups in England. As expected, the number of suspected ADR reports received so far during the 2nd year of the programme are reduced relative to the marked increase in exposure.

[3] Based on UK-wide vaccine uptake data up to the end of 2009. As the Yellow Card data are up to the present date, the available uptake data should not be used to derive adverse reaction reporting rates (as this will result in an over-estimation)

A. Injection-site reactions

Injection-site reactions including redness, pain and swelling are recognised side-effects of Cervarix vaccine and are listed in the product information. These may occur at a frequency[4] of more than 1 in 10 persons vaccinated. The reported cases of 'Pain in extremity' mainly relate to a sore arm.

The cases reported to the MHRA during use of the vaccine in the UK do not indicate any change in the severity or nature of injection-site reactions.

Reported event (Preferred Term[2])	Number of cases
Pain in extremity	438
Injection site swelling	107
Limb discomfort	104
Oedema peripheral	101
Hypoaesthesia	89
Injection site pain	77
Injection site erythema	70
Erythema	44
Paraesthesia	33
Skin discolouration	32
Injection site rash	26
Injection site reaction	25
Pain	23
Musculoskeletal stiffness	20
Local reaction	19
Peripheral coldness	19
Injection site inflammation	16
Injection site mass	15
Local swelling	15
Contusion	14
Injection site warmth	14
Sensation of heaviness	12
Rash macular	10
Injection site pruritus	9
Feeling cold	8
Injection site induration	8
Injection site nodule	8
Swelling	8
Injection site anaesthesia	7
Injection site haematoma	7
Livedo reticularis	7
Muscular weakness	6
Myalgia	6
Neck pain	6
Rash	6
Cyanosis	4
Feeling abnormal	4
Feeling hot	4
Injection site infection	4
Pallor	4
Pruritus	4
Sensory disturbance	4

[4] Based on clinical trial data

Asthenia	3
Injection site discharge	3
Injection site discolouration	3
Injection site urticaria	3
Limb immobilisation	3
Musculoskeletal pain	3
Poor peripheral circulation	3
Sensory loss	3
Tenderness	3
Dry skin	2
Grip strength decreased	2
Inflammation	2
Injected limb mobility decreased	2
Injection site cellulitis	2
Injection site irritation	2
Injection site vesicles	2
Skin reaction	2
Blister	1
Complex regional pain syndrome	1
Extensive swelling of vaccinated limb	1
Hypokinesia	1
Immobile	1
Impetigo	1
Injection site abscess	1
Injection site discomfort	1
Injection site haemorrhage	1
Injection site joint movement impairment	1
Injection site joint pain	1
Injection site movement impairment	1
Injection site papule	1
Injection site paraesthesia	1
Injection site scab	1
Joint swelling	1
Muscle spasms	1
Muscle tightness	1
Nausea	1
Nodule	1
Pain of skin	1
Peripheral vascular disorder	1
Rash maculo-papular	1
Rash pruritic	1
Scab	1
Sensation of pressure	1
Skin warm	1
Tremor	1
Urticaria	1
Total reactions	**1509**
Total reports	**1027**

B. Allergic reactions (including skin reactions not directly related to an injection-site reaction)

Allergic reactions are recognised side-effect of Cervarix vaccine and are listed in the product information. These may occur at a frequency[4] between 1 in 10 persons (for non-serious types of allergic reaction such as rash and itching) to less than 1 in 10,000 persons vaccinated. Severe allergic reactions are very rare.

The cases reported to the MHRA during use of the vaccine in the UK do not indicate any change in the severity or nature of allergic reactions.

Reported event (Preferred Term[2])	Number of cases
Rash	122
Urticaria	82
Pruritus	55
Erythema	41
Swelling face	39
Anaphylactic reaction	38
Dyspnoea	31
Rash generalised	30
Rash pruritic	30
Oedema peripheral	29
Lip swelling	25
Rash macular	23
Hypersensitivity	22
Dizziness	21
Eye swelling	17
Paraesthesia oral	17
Malaise	15
Throat tightness	14
Swollen tongue	12
Chest discomfort	10
Rash erythematous	10
Flushing	9
Pruritus generalised	9
Feeling hot	8
Pallor	8
Dermatitis allergic	7
Fatigue	7
Oropharyngeal pain	7
Paraesthesia	7
Pharyngeal oedema	7
Angioedema	6
Headache	6
Inflammation	6
Pyrexia	6
Throat irritation	6
Hyperventilation	5
Vomiting	5
Wheezing	5
Anaphylactic shock	4

Blister	4
Dysphagia	4
Hypoaesthesia	4
Hypoaesthesia oral	4
Nausea	4
Pain in extremity	4
Syncope	4
Eyelid oedema	3
Eye pruritus	3
Hyperhidrosis	3
Laryngeal oedema	3
Limb discomfort	3
Local swelling	3
Nasopharyngitis	3
Ocular hyperaemia	3
Pain	3
Petechiae	3
Rash maculo-papular	3
Skin reaction	3
Somnolence	3
Swelling	3
Vision blurred	3
Abdominal pain	2
Abdominal pain upper	2
Body temperature increased	2
Cold sweat	2
Dermatitis contact	2
Face oedema	2
Feeling cold	2
Heart rate increased	2
Heart rate irregular	2
Peripheral coldness	2
Skin discolouration	2
Skin disorder	2
Skin irritation	2
Tachycardia	2
Type i hypersensitivity	2
Anaphylactoid reaction	1
Asthenia	1
Asthenopia	1
Asthma	1
Back pain	1
Bronchospasm	1
Chest pain	1
Chills	1
Condition aggravated	1
Confusional state	1
Conjunctival hyperaemia	1
Convulsion	1
Cough	1
Dermatitis	1
Dry throat	1
Eczema	1
Eyelid disorder	1

Eyes sunken	1
Feeling abnormal	1
Feeling jittery	1
Generalised erythema	1
Gingival swelling	1
Hypersomnia	1
Hypertension	1
Increased bronchial secretion	1
Infusion site swelling	1
Injection site inflammation	1
Lip ulceration	1
Local reaction	1
Loss of consciousness	1
Migraine	1
Muscle tightness	1
Musculoskeletal stiffness	1
Mydriasis	1
Neck pain	1
Oedema mouth	1
Oral discomfort	1
Oral pain	1
Palpitations	1
Periorbital oedema	1
Photophobia	1
Piloerection	1
Pulse absent	1
Purpura	1
Rash follicular	1
Rash papular	1
Respiratory rate increased	1
Sneezing	1
Speech disorder	1
Systemic lupus erythematosus rash	1
Tenderness	1
Thirst	1
Tremor	1
Visual impairment	1
Total reactions	**958**
Total reports	**484**

C. 'Psychogenic' events

Psychogenic events including vasovagal syncope, faints and panic attacks can occur with any injection procedure, not just vaccination, and can be common in adolescents. These are due to fear and/or anticipation of the needle injection and are **not side-effects of Cervarix vaccine** as such. Such events can be associated with a wide range of temporary signs and symptoms including loss of consciousness, vision disturbance, injury, limb jerking (often misinterpreted as a seizure/convulsion), limb numbness or tingling, difficulty in breathing, hyperventilation etc.

The events in the list below were considered 'psychogenic' in nature based on MHRA assessment of the individual case details reported. The reported cases which do not refer specifically to vasovagal syncope, faint or panic attack (e.g. convulsion, transient blindness which refers to temporary loss of

vision at the start of a faint) were concurrently reported as signs or symptom of the psychogenic event; **i.e. these also were not side-effects of the vaccine itself**.

Reported event (Preferred Term[2])	Number of cases
Dizziness	307
Syncope	287
Nausea	147
Headache	107
Pallor	106
Vomiting	76
Malaise	72
Tremor	58
Vision blurred	46
Feeling hot	44
Flushing	40
Cold sweat	35
Hyperhidrosis	23
Presyncope	22
Hyperventilation	21
Loss of consciousness	19
Chills	17
Paraesthesia	17
Dyspnoea	16
Pyrexia	16
Somnolence	16
Convulsion	15
Fatigue	15
Heart rate increased	14
Muscle twitching	13
Rash	13
Unresponsive to stimuli	13
Asthenia	12
Feeling cold	12
Hypoaesthesia	12
Panic attack	12
Chest discomfort	11
Dyskinesia	11
Eye rolling	11
Tachycardia	11
Tearfulness	10
Erythema	9
Nervousness	9
Rash macular	9
Abdominal pain	8
Chest pain	8
Peripheral coldness	8
Abdominal pain upper	7
Hypotension	7
Lethargy	7
Muscular weakness	7
Photophobia	7
Visual impairment	7
Confusional state	6

Deafness	6
Fall	6
Feeling of body temperature change	6
Muscle rigidity	6
Musculoskeletal stiffness	6
Mydriasis	6
Nasopharyngitis	6
Throat tightness	6
Anxiety	5
Dizziness postural	5
Dysgeusia	5
Feeling abnormal	5
Skin discolouration	5
Urticaria	5
Blindness transient	4
Body temperature increased	4
Decreased appetite	4
Hot flush	4
Migraine	4
Muscle spasms	4
Panic reaction	4
Pulse abnormal	4
Tinnitus	4
Urinary incontinence	4
Abasia	3
Abdominal discomfort	3
Agitation	3
Balance disorder	3
Blindness	3
Blood pressure decreased	3
Cyanosis	3
Disorientation	3
Disturbance in attention	3
Dysstasia	3
Emotional disorder	3
Feeling drunk	3
Hearing impaired	3
Heart rate irregular	3
Hypoventilation	3
Pain	3
Pain in extremity	3
Respiratory rate increased	3
Sensory loss	3
Throat irritation	3
Vertigo	3
Amnesia	2
Body temperature decreased	2
Bradycardia	2
Circulatory collapse	2
Colour blindness acquired	2
Consciousness fluctuating	2
Diplopia	2
Dry mouth	2
Dry throat	2

Dysarthria	2
Dysphagia	2
Heart rate decreased	2
Hypertension	2
Hypoacusis	2
Myalgia	2
Neck pain	2
Oropharyngeal pain	2
Paraesthesia oral	2
Procedural dizziness	2
Pruritus	2
Pulse pressure decreased	2
Pupil fixed	2
Rash generalised	2
Retching	2
Salivary hypersecretion	2
Shock	2
Abdominal distension	1
Abnormal behaviour	1
Altered state of consciousness	1
Aphasia	1
Asthma	1
Blood pressure increased	1
Blood pressure systolic decreased	1
Bruxism	1
Burning sensation	1
Cough	1
Deafness transitory	1
Depressed level of consciousness	1
Discomfort	1
Dissociation	1
Ear discomfort	1
Ear pain	1
Emotional distress	1
Epistaxis	1
Eyelid oedema	1
Eye pain	1
Face injury	1
Facial spasm	1
Fear	1
Feeling of despair	1
Foaming at mouth	1
Gait disturbance	1
Grand mal convulsion	1
Grip strength decreased	1
Head banging	1
Head discomfort	1
Heat rash	1
Hemiparesis	1
Hypersomnia	1
Hypoaesthesia facial	1
Hypokinesia	1
Hypotonia	1
Incontinence	1

Lip swelling	1
Livedo reticularis	1
Myoclonus	1
Nervous system disorder	1
Oral discomfort	1
Palpitations	1
Peripheral circulatory failure	1
Pharyngeal oedema	1
Poor peripheral circulation	1
Psychomotor hyperactivity	1
Respiratory arrest	1
Respiratory rate decreased	1
Seizure anoxic	1
Sensation of heaviness	1
Sinus tachycardia	1
Sleep attacks	1
Sudden onset of sleep	1
Tachypnoea	1
Total reactions	**2064**
Total reports	**809**

D. 'Other recognised' reactions

This section includes other events recognised to be side-effects of Cervarix vaccine and not already included in sections A and B above. This also includes signs and symptoms of recognised side effects. The frequencies, where known, are listed in the product information.

The cases reported to the MHRA during use of the vaccine in the UK so far do not indicate any change in the severity or nature of these reactions.

Reported event (Preferred Term[2])	**Number of cases**
Nausea	553
Dizziness	543
Headache	537
Vomiting	239
Malaise	197
Fatigue	170
Pyrexia	158
Abdominal pain	67
Abdominal pain upper	50
Diarrhoea	50
Myalgia	44
Feeling hot	42
Lethargy	39
Body temperature increased	33
Pain	30
Oropharyngeal pain	24
Arthralgia	23
Pallor	22
Asthenia	21
Chills	20

Influenza like illness	18
Lymphadenopathy	18
Pain in extremity	18
Somnolence	17
Abdominal discomfort	14
Flushing	13
Paraesthesia	13
Tremor	11
Rash	10
Decreased appetite	9
Neck pain	8
Feeling cold	7
Pruritus	7
Hyperhidrosis	6
Hypoaesthesia	6
Musculoskeletal stiffness	6
Back pain	5
Cough	5
Nasopharyngitis	5
Feeling of body temperature change	4
Migraine	4
Nervousness	4
Muscle fatigue	3
Muscular weakness	3
Cold sweat	2
Erythema	2
Feeling abnormal	2
Gait disturbance	2
Head discomfort	2
Hot flush	2
Joint swelling	2
Listless	2
Nasal congestion	2
Pruritus generalised	2
Skin warm	2
Throat irritation	2
Abdominal pain lower	1
Axillary mass	1
Bedridden	1
Body temperature	1
Body temperature fluctuation	1
Dyspnoea	1
Generalised erythema	1
Groin pain	1
Ill-defined disorder	1
Immunisation reaction	1
Induration	1
Insomnia	1
Local swelling	1
Loss of consciousness	1
Lower respiratory tract infection	1
Mobility decreased	1
Muscle spasms	1
Muscle twitching	1

Musculoskeletal chest pain	1
Musculoskeletal discomfort	1
Musculoskeletal pain	1
Night sweats	1
Peripheral coldness	1
Pharyngitis	1
Rash erythematous	1
Rash generalised	1
Respiratory disorder	1
Restlessness	1
Rhinorrhoea	1
Sensation of heaviness	1
Sudden onset of sleep	1
Swelling	1
Swelling face	1
Thirst	1
Throat tightness	1
Upper respiratory tract infection	1
Urticaria	1
Weight decreased	1
Total reactions	**3138**
Total reports	**1668**

E. Suspected adverse reactions not currently recognised

This section includes reports which, based on MHRA assessment of the case details provided, do not fit into one of the above 4 categories.

These suspected ADRs are not currently recognised as side effects of Cervarix vaccine and the available evidence does not suggest a causal link with the vaccine. These are isolated medical events which may have been coincidental with vaccination. These reports are continually assessed by the MHRA.

Guillain Barre Syndrome (GBS) naturally occurs in the population and is usually thought to be caused by a preceding infectious illness. More than 3.5 million doses of Cervarix have been given to girls and there is no evidence that the vaccine has increased the frequency of GBS above that expected to occur naturally in the population.

Encephalitis naturally occurs in the population and it is most often caused by a preceding viral infection. The four cases of encephalitis reported so far, amongst the several hundred thousand girls vaccinated, do not exceed the numbers normally expected in the absence of vaccination. There is therefore no suggestion at present that the vaccine can cause encephalitis.

Chronic fatigue syndrome (CFS) is not an uncommon condition amongst adolescents and rates are greater in females than in males. Given that more than 3.5 million doses of Cervarix have now been given in the UK, it is inevitable that conditions such as CFS will occur not long after vaccination regardless of any causal association with the vaccine.

MHRA has conducted an analysis of reported cases of CFS compared to the normal background frequency. This analysis shows that amongst the population of 12-13 yr old girls immunised so far in the UK, we would have expected to observe more than 70 new cases of CFS already, regardless of vaccination. We would also expect to have seen many more cases of chronic fatigue-like syndrome that have not necessarily met the diagnostic criteria for CFS amongst this population.

The Government's independent expert advisory Committee on vaccines and medicines safety, the Commission on Human Medicines (CHM), recently reviewed the cases of CFS, post-viral fatigue syndrome and cases that could possibly represent a chronic fatigue-like syndrome. They advised that the available evidence does not support a causal association between Cervarix vaccine and CFS, and the balance of risks and benefits of Cervarix remains positive. Cases of possible CFS will remain under close and continual review by the MHRA.

System Organ Class	Reported event (Preferred Term[2])	Number of cases
Blood and lymphatic system disorders	Anaemia	1
	Aplastic anaemia	1
	Eosinophilia	1
	Neutropenia	1
	Pancytopenia	1
Cardiac disorders	Cyanosis	4
	Palpitations	6
	Sinus tachycardia	1
	Tachycardia	1
Congenital, familial and genetic disorders	Arteriovenous malformation	1
	Cerebral palsy	1
	Cleft palate	1
	Heart disease congenital	1
	Hypospadias	1
	Limb malformation	1
	Pilonidal cyst congenital	1
Ear and labyrinth disorders	Deafness	1
	Deafness bilateral	1
	Ear discomfort	1
	Ear pain	6
	Hypoacusis	1
	Tinnitus	1
	Vertigo	2
Endocrine disorders	Adrenocortical insufficiency acute	1
Eye disorders	Accommodation disorder	1
	Conjunctival hyperaemia	1
	Dark circles under eyes	1
	Diplopia	2
	Dry eye	1
	Excessive eye blinking	1
	Eye disorder	1
	Eyelid oedema	1
	Eye pain	2
	Eye swelling	1
	Gaze palsy	1
	Mydriasis	3
	Photophobia	6
	Vision blurred	7
	Visual impairment	5
	Vitreous floaters	1

Gastrointestinal disorders	Abdominal discomfort	1
	Abdominal pain	10
	Abdominal pain lower	1
	Abdominal pain upper	2
	Abnormal faeces	1
	Colitis	1
	Colitis ulcerative	1
	Constipation	1
	Diarrhoea	7
	Diarrhoea haemorrhagic	1
	Flatulence	1
	Frequent bowel movements	1
	Gastrointestinal disorder	1
	Hypoaesthesia oral	1
	Intestinal functional disorder	1
	Irritable bowel syndrome	1
	Lip blister	1
	Lip swelling	1
	Mouth ulceration	2
	Nausea	24
	Paraesthesia oral	1
	Vomiting	15
General disorders and administration site conditions	Abasia	3
	Asthenia	8
	Axillary pain	1
	Chest discomfort	8
	Chest pain	15
	Chills	4
	Chronic fatigue syndrome	3
	Condition aggravated	3
	Fatigue	15
	Feeling abnormal	2
	Feeling cold	6
	Feeling hot	4
	Gait disturbance	2
	Hyperpyrexia	1
	Inflammation	1
	Influenza like illness	31
	Local swelling	2
	Malaise	17
	Oedema peripheral	4
	Pain	13
	Pyrexia	13
	Sensation of foreign body	1
	Sensation of pressure	1
	Swelling	1
	Systemic inflammatory response syndrome	1
Hepatobiliary disorders	Jaundice	1
Immune system disorders	Hypersensitivity	1
Infections and infestations	Abscess	1
	Acarodermatitis	1

	Anogenital warts	1
	Application site pustules	1
	Beta haemolytic streptococcal infection	1
	Bronchitis	1
	Folliculitis	1
	Furuncle	1
	Hepatitis viral	1
	Herpes zoster	2
	Hordeolum	1
	Infectious mononucleosis	3
	Influenza	2
	Kidney infection	1
	Laryngitis	1
	Lower respiratory tract infection	5
	Nasopharyngitis	5
	Otitis media	1
	Pharyngitis	2
	Pneumonia viral	1
	Post viral fatigue syndrome	6
	Respiratory tract infection	1
	Sepsis	1
	Severe acute respiratory syndrome	1
	Staphylococcal infection	1
	Streptococcal sepsis	1
	Urinary tract infection	2
	Varicella	1
	Viraemia	1
	Viral infection	7
Injury, poisoning and procedural complications	Contusion	4
	Drug exposure before pregnancy	2
	Drug exposure during pregnancy	12
	Fall	1
	Inappropriate schedule of drug administration	1
	Incorrect dose administered	1
	Wrong technique in drug usage process	1
Investigations	Alanine aminotransferase increased	1
	Blood cortisol decreased	1
	Blood glucose increased	4
	Blood pressure increased	1
	Body temperature increased	2
	Cell marker increased	1
	Csf cell count increased	1
	Heart rate decreased	1
	Neurological examination	1

	abnormal	
	Neutrophil count decreased	1
	Peak expiratory flow rate decreased	1
	Radial pulse	1
	Respiratory rate increased	1
	Weight decreased	4
	Weight increased	2
Metabolism and nutrition disorders	Decreased appetite	8
	Dehydration	2
	Diabetes mellitus inadequate control	1
	Diabetic ketoacidosis	1
	Hypoglycaemia	1
	Increased appetite	1
	Type 1 diabetes mellitus	1
Musculoskeletal and connective tissue disorders	Arthralgia	19
	Arthritis	1
	Arthritis reactive	1
	Arthropathy	1
	Back pain	14
	Bone pain	1
	Flank pain	1
	Groin pain	2
	Joint stiffness	1
	Joint swelling	1
	Mobility decreased	1
	Muscle rigidity	1
	Muscle spasms	2
	Muscle twitching	3
	Muscular weakness	13
	Musculoskeletal chest pain	1
	Musculoskeletal pain	2
	Musculoskeletal stiffness	5
	Myalgia	9
	Neck pain	6
	Osteitis	1
	Pain in extremity	23
	Palindromic rheumatism	1
	Rheumatoid arthritis	1
	Sensation of heaviness	4
	Weight bearing difficulty	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukaemia	1
	Benign hydatidiform mole	1
	Neoplasm malignant	1
Nervous system disorders	Aphasia	1
	Aphonia	3
	Areflexia	1
	Ataxia	1
	Balance disorder	2
	Burning sensation	1

	Complex regional pain syndrome	2
	Convulsion	22
	Coordination abnormal	1
	Crying	2
	Depressed level of consciousness	1
	Diplegia	2
	Disturbance in attention	2
	Dizziness	29
	Dizziness postural	1
	Drooling	2
	Dysarthria	5
	Dysgeusia	1
	Dyskinesia	4
	Dysstasia	3
	Encephalitis	3
	Epilepsy	6
	Facial palsy	4
	Facial paresis	2
	Grand mal convulsion	5
	Guillain-barre syndrome	4
	Headache	43
	Head discomfort	3
	Hemiparesis	2
	Hypertonia	1
	Hypoaesthesia	24
	Ivth nerve paralysis	1
	Lethargy	16
	Loss of consciousness	9
	Meningism	1
	Migraine	14
	Migraine with aura	1
	Monoplegia	1
	Movement disorder	1
	Myoclonic epilepsy	1
	Optic neuritis	1
	Paraesthesia	18
	Paralysis	1
	Petit mal epilepsy	2
	Presyncope	1
	Psychomotor hyperactivity	1
	Radiculitis brachial	1
	Sedation	1
	Sensory disturbance	6
	Sensory loss	2
	Somnolence	13
	Speech disorder	1
	Status epilepticus	1
	Syncope	28
	Tremor	12
	Unresponsive to stimuli	3
	Visual field defect	3
Pregnancy, puerperium	Abortion spontaneous	9

and perinatal conditions	Live birth	1
	Pregnancy with injectable contraceptive	1
	Premature baby	3
Psychiatric disorders	Abnormal behaviour	1
	Abnormal sleep-related event	1
	Acute psychosis	1
	Aggression	1
	Anxiety	4
	Confusional state	3
	Depressed mood	1
	Depression	1
	Disorientation	2
	Dysphemia	1
	Eating disorder	1
	Emotional disorder	2
	Emotional distress	1
	Fear	1
	Hallucination	6
	Hallucination, auditory	1
	Hallucination, visual	1
	Hypomania	1
	Insomnia	6
	Paranoia	1
	Psychiatric symptom	1
	Psychotic disorder	1
	Screaming	1
	Sleep disorder	2
	Somatisation disorder	1
	Tearfulness	3
Renal and urinary disorders	Neurogenic bladder	1
	Pollakiuria	1
	Urinary incontinence	2
	Urinary retention	2
Reproductive system and breast disorders	Amenorrhoea	7
	Breast pain	1
	Breast swelling	1
	Breast tenderness	1
	Cervix inflammation	1
	Dysmenorrhoea	3
	Menorrhagia	4
	Menstrual disorder	1
	Menstruation delayed	2
	Menstruation irregular	2
	Metrorrhagia	1
	Vaginal discharge	1
	Vaginal haemorrhage	7
	Vaginal lesion	1
	Vulval ulceration	1
Respiratory, thoracic and mediastinal disorders	Asthma	7
	Cough	7
	Dyspnoea	18
	Epistaxis	8

	Haemoptysis	2
	Hyperventilation	1
	Hypoventilation	1
	Increased upper airway secretion	1
	Oropharyngeal blistering	1
	Oropharyngeal pain	10
	Productive cough	1
	Rhinorrhoea	2
	Throat tightness	1
	Upper airway obstruction	1
	Wheezing	4
Skin and subcutaneous tissue disorders	Acne	1
	Alopecia	8
	Alopecia areata	2
	Angioedema	2
	Blister	4
	Cold sweat	1
	Dermatitis allergic	1
	Eczema	5
	Eczema vesicular	1
	Erythema	2
	Erythema multiforme	5
	Guttate psoriasis	1
	Henoch-schonlein purpura	1
	Hyperhidrosis	3
	Hypoaesthesia facial	7
	Livedo reticularis	1
	Photosensitivity reaction	1
	Psoriasis	1
	Rash	4
	Rash generalised	2
	Rash maculo-papular	1
	Rash vesicular	1
	Skin discolouration	3
	Skin exfoliation	2
	Skin hypertrophy	1
	Skin irritation	1
	Skin lesion	1
	Stevens-johnson syndrome	1
	Swelling face	2
	Trichorrhexis	1
	Urticaria	2
	Urticaria chronic	3
Surgical and medical procedures	Abortion induced	1
Vascular disorders	Circulatory collapse	2
	Deep vein thrombosis	1
	Flushing	1
	Haemorrhage	2
	Hot flush	2
	Hypotension	3

	Pallor	3
	Peripheral coldness	9
Total reactions		**1129**
Total reports		**580**

In relation to safety in pregnancy, during pre-licensing studies of Cervarix it was found that almost 3,696 women became pregnant before or after receiving the vaccine. The overall rates of spontaneous abortion in these clinical trials were no greater than the background rates in the general population (i.e. regardless of vaccination). There is currently no evidence to suggest that Cervarix vaccine carries any risks during pregnancy. Nonetheless, Cervarix is not recommended for use in pregnancy.

ANNEXE 2

'Gardasil' Suspected Adverse Reaction Analysis

Safeguarding public health

Suspected Adverse Reaction Analysis

GARDASIL Human papillomavirus (HPV) vaccine

13 May 2010

This report summarises the adverse reactions suspected to have been caused by Gardasil human papillomavirus (HPV) vaccine in the UK. This includes reports received between 13 December 2006 and 12 May 2010. These reports have been voluntarily submitted to the MHRA by healthcare professionals and members of the public via the Yellow Card Scheme (visit www.yellowcard.gov.uk) and by the manufacturers of the vaccine as part of their legal requirements

It is essential to bear in mind that reports to the MHRA relate only to adverse medical events which the reporter considered could have been caused by the vaccine (i.e. if there was merely a **suspicion** of causality). Therefore, cases may be true side-effects or they may have been purely coincidental events due to underlying or undiagnosed illness that would have occurred anyway in the absence of vaccination. Events may also have been psychogenic[1] in origin. This report therefore cannot be considered to represent a list of known side-effects of the vaccine. These data also cannot be used to determine the frequency, or incidence, of known side-effects because they are often under-reported. The known side-effects, and their frequencies (based on clinical trial data), are available in the product information (see http://emc.medicines.org.uk/).

The reactions in this report have been broken down into 5 categories based on scientific assessment of individual cases by MHRA assessors: injection-site reactions; allergic reactions; 'psychogenic' events; other recognised reactions; and 'suspected adverse reactions not currently recognised' (reactions in this latter category are divided into the high-level classification of System Organ Class)[2].

A single report may contain more than one reaction, more than one sign or symptom of a single reaction or reactions in more than one of the above categories. Therefore the total number of listed reactions is greater than the total number of reports and total reports in each of the 5 tables should not be added together.

Headline summary:

To date, half of the suspected ADRs reported to MHRA in association with Gardasil vaccine have related either to the signs and symptoms of recognised side effects listed in the product information or were due to the injection process and not the vaccine itself (i.e. 'psychogenic' in nature).

For the isolated cases of other medical conditions reported, the available evidence does not suggest that the vaccine caused the condition and these may have been coincidental events.

The balance of risks and benefits of Gardasil remains positive.

[1] For this analysis, defined as non-allergic events which occurred within minutes of, or soon after, vaccination and were most likely a psychogenic response to, or anticipation of, the injection. These are not side effects to the vaccine as such and can occur with any needle injection procedure.
[2] Using MedDRA terminology

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SUMMARY OF UK SAFETY EXPERIENCE

Total number of reports received: 69
Total number of suspected reactions: 166

A. Injection-site reactions

Injection-site reactions including redness, pain and swelling are recognised side-effects of Gardasil vaccine and are listed in the product information. These may occur at a frequency[3] of more than 1 in 10 persons vaccinated.

The cases reported to the MHRA during use of the vaccine in the UK do not indicate any change in the severity or nature of injection-site reactions.

Reported event (Preferred Term[2])	Number of cases
Injection site pain	2
Injection site swelling	2
Hypoaesthesia	2
Inflammation	1
Injection site erythema	1
Oedema peripheral	1
Pain	1
Swelling	1
Musculoskeletal stiffness	1
Myalgia	1
Pain in extremity	1
Burning sensation	1
Paraesthesia	1
Erythema	1
Skin reaction	1
Peripheral coldness	1
Total reactions	**19**
Total reports	**10**

B. Allergic reactions (including skin reactions not directly related to an injection-site reaction)

Allergic reactions are recognised side-effect of Gardasil vaccine and are listed in the product information. These may occur at a frequency[3] between 1 in 10 persons (for non-serious types of allergic reaction such as rash and itching) to less than 1 in 10,000 persons vaccinated. Severe allergic reactions are very rare.

The cases reported to the MHRA during use of the vaccine in the UK do not indicate any change in the severity or nature of allergic reactions.

Reported event (Preferred Term[2])	Number of cases
Urticaria	7
Paraesthesia oral	1
Swollen tongue	1
Feeling of body temperature change	1

[3] Based on clinical trial data

Local reaction	1
Oedema peripheral	1
Anaphylactic reaction	1
Crying	1
Panic reaction	1
Dyspnoea	1
Angioedema	1
Dermatitis allergic	1
Pruritus	1
Pruritus generalised	1
Rash	1
Rash maculo-papular	1
Rash papular	1
Total reactions	**23**
Total reports	**14**

C. 'Psychogenic' events

Psychogenic events including vasovagal syncope, faints and panic attacks can occur with any injection procedure, not just vaccination, and can be common in adolescents. These are due to fear and/or anticipation of the needle injection and are not side-effects of Gardasil vaccine as such. Such events can be associated with a wide range of temporary signs and symptoms including loss of consciousness, vision disturbance, injury, limb jerking (often misinterpreted as a seizure/convulsion), limb numbness or tingling, difficulty in breathing, hyperventilation etc.

The events in the list below were considered 'psychogenic' in nature based on MHRA assessment of the individual case details reported. The cases which do not refer specifically to vasovagal syncope, faint or panic attacks (e.g. convulsion) were concurrently reported as a signs or symptom of the psychogenic event; i.e. these also were not side-effects to the vaccine itself.

Reported event (Preferred Term[2])	**Number of cases**
Syncope	6
Convulsion	2
Pallor	2
Asthenia	1
Blood pressure immeasurable	1
Pulse pressure decreased	1
Muscle twitching	1
Dizziness	1
Loss of consciousness	1
Somnolence	1
Hypoventilation	1
Hypotension	1
Total reactions	**19**
Total reports	**9**

D. 'Other recognised' reactions

This section includes other events recognised to be side-effects of Gardasil vaccine and not already included in sections A and B above. This also includes signs and symptoms of recognised side effects. The frequencies, where known, are listed in the product information.

The cases reported to the MHRA during use of the vaccine in the UK so far do not indicate any change in the severity or nature of these reactions.

Reported event (Preferred Term[2])	Number of cases
Headache	5
Pyrexia	4
Nausea	3
Vomiting	3
Myalgia	3
Dizziness	3
Pain	2
Photophobia	1
Abdominal pain upper	1
Diarrhoea	1
Fatigue	1
Feeling hot	1
Dizziness postural	1
Erythema	1
Headache	5
Total reactions	**30**
Total reports	**14**

E. 'Suspected adverse reactions not currently recognised'

This section includes reports which, based on MHRA assessment of the case details provided, do not fit into one of the above 4 categories.

These suspected ADRs are not currently recognised as side effects of Gardasil vaccine and the available evidence does not suggest a causal link with the vaccine. These are isolated medical events which may have been coincidental with vaccination. These reports are continually assessed by the MHRA.

System Organ Class	Reported event (Preferred Term[2])	Number of cases
Blood and lymphatic system disorders	Anaemia	1
	Coagulopathy	1
Gastrointestinal disorders	Abdominal pain	1
	Colitis ulcerative	1
	Diarrhoea	2
	Gingivitis	1
	Irritable bowel syndrome	1
	Mouth ulceration	1
	Nausea	2
	Oesophageal mucosal hyperplasia	1
	Paraesthesia oral	1
	Vomiting	1
	Vomiting projectile	1
General disorders and administration site conditions	Asthenia	1
	Drug ineffective	1
	Fatigue	1
	Oedema peripheral	2
Infections and	Anogenital warts	1

infestations	Beta haemolytic streptococcal infection	1
	Chorioamnionitis	1
	Gastrointestinal infection	1
	Herpes zoster	1
	Influenza	1
	Papilloma viral infection	1
Investigations	Blood albumin abnormal	1
	Blood pressure increased	1
	Protein total abnormal	1
	Smear cervix abnormal	1
	Vitamin B12 increased	1
	Weight decreased	1
Metabolism and nutrition disorders	Decreased appetite	1
	Dehydration	1
	Lactose intolerance	1
Musculoskeletal and connective tissue disorders	Arthralgia	2
	Arthritis reactive	2
	Joint stiffness	1
	Joint swelling	1
Nervous system disorders	Convulsion	1
	Dizziness	1
	Grand mal convulsion	1
	Headache	1
	Hypoaesthesia	2
	Lethargy	1
	Movement disorder	1
	Paraesthesia	3
	Peripheral sensory neuropathy	1
	Syncope	1
Pregnancy, puerperium and perinatal conditions	Abortion threatened	1
	Cervical incompetence	1
	Premature baby	1
	Premature labour	1
Psychiatric disorders	Bipolar disorder	1
Reproductive system and breast disorders	Cervical dysplasia	1
	Menorrhagia	1
	Vaginal haemorrhage	1
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	1
	Pharyngeal erythema	1
Skin and subcutaneous tissue disorders	Alopecia effluvium	1
	Eczema	1
	Erythema	1
	Hyperhidrosis	1
	Rash	2
	Skin discolouration	1
	Skin exfoliation	1
	Skin hypertrophy	1
Vascular disorders	Pallor	1
Total reactions		**75**
Total reports		**33**

ANNEXE 3

Human Papillomavirus Vaccine (brand unspecified)
Suspected Adverse Reaction Analysis

Safeguarding public health

Suspected Adverse Reaction Analysis

Human papillomavirus (HPV) vaccine (brand unspecified)

13 May 2010

This report summarises the reports of adverse reactions suspected to have been caused by human papillomavirus (HPV) vaccine for which information on the specific brand administered (whether Cervarix or Gardasil) is currently unavailable. This includes reports received up to 12 May 2010. Separate Adverse Reaction Analysis summaries exist for reports in which the brand was stated. These reports have been voluntarily submitted to the MHRA by healthcare professionals and members of the public via the Yellow Card Scheme (visit www.yellowcard.gov.uk) and by the manufacturers of the vaccine as part of their legal requirements.

It is essential to bear in mind that reports to the MHRA relate only to adverse medical events which the reporter considered could have been caused by the vaccine (i.e. if there was merely a **suspicion** of causality). Therefore, cases may be true side-effects or they may have been purely coincidental events due to underlying or undiagnosed illness that would have occurred anyway in the absence of vaccination. Events may also have been psychogenic[1] in origin. This report therefore cannot be considered to represent a list of known side-effects of the vaccine. These data also cannot be used to determine the frequency, or incidence, of known side-effects because they are often under-reported. The known side-effects, and their frequencies (based on clinical trial data), are available in the product information (see http://emc.medicines.org.uk/).

The reactions in this report have been broken down into 5 categories based on scientific assessment of individual cases by MHRA assessors: injection-site reactions; allergic reactions; 'psychogenic' events; other recognised reactions; and 'suspected adverse reactions not currently recognised' (reactions in this latter category are divided into the high-level classification of System Organ Class)[2]. The same event term may appear in more than one category (e.g. 'rash' may be associated with injection site, allergic or unrecognised suspected reactions and 'psychogenic' events). However, an event from a single report will appear in only one category.

A single report may contain more than one reaction, more than one sign or symptom of a single reaction or different reactions in more than one of the above categories. Therefore the total number of listed reactions is greater than the total number of reports and total reports in each of the 5 tables should not be added together.

Headline summary:

To date, most suspected ADRs reported to MHRA in association with HPV vaccine have related to the signs and symptoms of recognised side effects listed in the product information or were due to the injection process and not the vaccine itself (i.e. 'psychogenic' in nature such as faints).

For the isolated case of other medical conditions reported, the available evidence does not suggest that the vaccine caused the condition and these may have been coincidental events.

Following administration of more than 3.5 million doses across the UK since September 2008, the balance of risks and benefits of Cervarix remains positive

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[1] For this analysis, defined as non-allergic events which occurred within minutes of, or soon after, vaccination and were most likely a psychogenic response to, or anticipation of, the injection. These are not side effects to the vaccine as such and can occur with any needle injection procedure.

[2] Using MedDRA terminology

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SUMMARY OF UK SAFETY EXPERIENCE

Total number of reports received: 229
Total number of suspected reactions: 679
Estimated number of doses of Cervarix administered across the UK: at least 3.5 million doses[3]

A. Injection-site reactions

Injection-site reactions including redness, pain and swelling are recognised[4] side-effects of HPV vaccines and are listed in the product information. These may occur at a frequency[5] of more than 1 in 10 persons vaccinated.

The cases reported to the MHRA during use of the vaccine in the UK do not indicate any change in the severity or nature of injection site reactions.

Reported event (Preferred Term[2])	Number of cases
Pain in extremity	14
Oedema peripheral	8
Injection site erythema	5
Injection site swelling	5
Pain	5
Erythema	4
Musculoskeletal stiffness	4
Feeling hot	3
Injection site reaction	3
Injection site coldness	2
Injection site discolouration	2
Injection site mass	2
Injection site pain	2
Peripheral coldness	2
Pruritus	2
Sensory loss	2
Skin discolouration	2
Skin reaction	2
Tenderness	2
Hyperaesthesia	1
Hypoaesthesia	1
Injection site anaesthesia	1
Injection site haematoma	1
Injection site haemorrhage	1
Injection site rash	1
Limb immobilisation	1
Local reaction	1
Local swelling	1
Lymphoedema	1
Mass	1

[3] Based on UK-wide vaccine uptake data up to the end of 2009. As the Yellow Card data are up to the present date, the available uptake data should not be used to derive adverse reaction reporting rates (as this will result in an over-estimation)
[4] Known to be associated with either Cervarix or Gardasil
[5] Based on clinical trial data

Mobility decreased	1
Musculoskeletal pain	1
Paraesthesia	1
Rash	1
Urticaria	1
Total reactions	**87**
Total reports	**47**

B. Allergic reactions (including skin reactions not directly related to an injection-site reaction)

Allergic reactions are a recognised[4] side-effect of HPV vaccines and are listed in the product information. These may occur at a frequency[5] between 1 in 10 persons (for non-serious types of allergic reaction such as rash and itching) to less than 1 in 10,000 persons vaccinated. Severe allergic reactions are very rare.

The cases reported to the MHRA during use of the vaccine in the UK do not indicate any change in the severity or nature of allergic reactions.

Reported event (Preferred Term[2])	**Number of cases**
Rash	11
Urticaria	8
Dyspnoea	5
Eyelid oedema	4
Hypersensitivity	4
Dermatitis allergic	3
Erythema	3
Rash erythematous	3
Rash macular	3
Rash pruritic	3
Anaphylactic reaction	2
Blister	2
Dizziness	2
Heat rash	2
Lip swelling	2
Pharyngeal oedema	2
Pruritus	2
Swollen tongue	2
Contusion	1
Dysphagia	1
Eczema	1
Fatigue	1
Feeling hot	1
Headache	1
Laryngeal oedema	1
Lethargy	1
Myalgia	1
Nausea	1
Oedema mouth	1
Paraesthesia oral	1

Pyrexia	1
Rash generalised	1
Somnolence	1
Stridor	1
Swelling	1
Swelling face	1
Throat irritation	1
Throat tightness	1
Type iv hypersensitivity reaction	1
Urticaria pigmentosa	1
Vomiting	1
Total reactions	**86**
Total reports	**47**

C. 'Psychogenic' events

Psychogenic events including vasovagal syncope, faints and panic attacks can occur with any injection procedure, not just vaccination, and can be common in adolescents. These are due to fear and/or anticipation of the needle injection and are not side-effects of HPV vaccine as such. Such events can be associated with a wide range of temporary signs and symptoms including loss of consciousness, vision disturbance, injury, limb jerking (often misinterpreted as a seizure/convulsion), limb numbness or tingling, difficulty in breathing, hyperventilation etc.

Reported event (Preferred Term[2])	**Number of cases**
Syncope	26
Dizziness	15
Headache	9
Pallor	5
Vomiting	4
Dyspnoea	3
Nausea	3
Rash	3
Somnolence	3
Blood pressure increased	2
Heart rate increased	2
Hyperventilation	2
Malaise	2
Muscular weakness	2
Presyncope	2
Vision blurred	2
Abasia	1
Abdominal discomfort	1
Abdominal pain	1
Asthenia	1
Back pain	1
Blindness transient	1
Body temperature decreased	1
Chills	1
Convulsion	1
Disturbance in attention	1

Dry mouth	1
Dyskinesia	1
Fatigue	1
Heart rate irregular	1
Hot flush	1
Hyperhidrosis	1
Hypoaesthesia	1
Migraine	1
Paraesthesia	1
Photophobia	1
Pruritus	1
Pyrexia	1
Sensory loss	1
Tremor	1
Urticaria	1
Visual impairment	1
Total reactions	**111**
Total reports	**46**

D. 'Other recognised' reactions

This section includes other events recognised[4] to be side-effects of HPV vaccine and not already included in sections A and B above. This also includes signs and symptoms of recognised side effects. The frequencies, where known, are listed in the product information.

The cases reported to the MHRA during use of the vaccine in the UK so far do not indicate any change in the severity or nature of these reactions.

Reported event (Preferred Term[2])	**Number of cases**
Nausea	26
Headache	24
Malaise	21
Pyrexia	20
Dizziness	13
Vomiting	13
Fatigue	11
Abdominal pain	6
Lethargy	6
Abdominal pain upper	5
Myalgia	4
Asthenia	3
Body temperature increased	3
Decreased appetite	3
Diarrhoea	3
Somnolence	3
Back pain	2
Limb discomfort	2
Musculoskeletal stiffness	2
Oropharyngeal pain	2
Abdominal pain lower	1

Arthralgia	1
Body temperature fluctuation	1
Dizziness postural	1
Feeling of body temperature change	1
Gastrointestinal disorder	1
Hot flush	1
Hypoaesthesia	1
Influenza like illness	1
Local reaction	1
Lymphadenopathy	1
Neck pain	1
Pain	1
Pain in extremity	1
Respiratory tract infection	1
Total reactions	**187**
Total reports	**76**

E. 'Suspected adverse reactions not currently recognised'

This section includes reports which, based on MHRA assessment of the case details provided, do not fit into one of the above 4 categories.

These suspected ADRs are not currently recognised as side effects of Cervarix vaccine and the available evidence does not suggest a causal link with the vaccine. These are isolated medical events which may have been coincidental with vaccination. These reports are continually assessed by the MHRA.

System Organ Class	Reported event (Preferred Term[2])	Number of cases
Ear and labyrinth disorders	Ear pain	2
	Hyperacusis	1
Endocrine disorders	Adrenocortical insufficiency acute	1
Eye disorders	Eye discharge	1
	Eye pain	1
	Photopsia	1
	Vision blurred	6
	Visual impairment	2
Gastrointestinal disorders	Abdominal discomfort	1
	Abdominal pain	5
	Abdominal pain upper	1
	Diarrhoea	1
	Gingival disorder	1
	Nausea	4
	Vomiting	1
General disorders and administration site conditions	Abasia	2
	Asthenia	1
	Chest pain	1
	Chills	1
	Condition aggravated	1
	Discomfort	1

	Exercise tolerance decreased	1
	Fatigue	8
	Feeling abnormal	1
	Feeling cold	2
	Gait disturbance	2
	Influenza like illness	8
	Local swelling	1
	Malaise	2
	Oedema peripheral	1
	Pain	1
	Pyrexia	3
	Temperature intolerance	1
	Tenderness	1
	Thirst	1
Infections and infestations	Herpes zoster	1
	Infection	1
	Labyrinthitis	1
	Skin infection	1
Injury, poisoning and procedural complications	Axillary nerve injury	1
Investigations	Body temperature increased	1
	Weight decreased	1
Metabolism and nutrition disorders	Decreased appetite	1
	Diabetes mellitus inadequate control	1
	Hyperglycaemia	1
Musculoskeletal and connective tissue disorders	Arthralgia	4
	Back pain	1
	Joint stiffness	1
	Muscle twitching	1
	Muscular weakness	2
	Musculoskeletal stiffness	2
	Pain in extremity	2
Nervous system disorders	Balance disorder	1
	Chorea	1
	Complex regional pain syndrome	2
	Convulsion	3
	Dizziness	12
	Dizziness postural	2
	Dyskinesia	1
	Epilepsy	3
	Facial palsy	1
	Grand mal convulsion	2
	Headache	11
	Hypoaesthesia	7
	Lethargy	4
	Loss of consciousness	2
	Migraine	1
	Neuritis	1
	Paraesthesia	6
	Sensory loss	1
	Somnolence	1
	Syncope	7

	Tremor	3
Psychiatric disorders	Confusional state	2
	Depression	1
	Dissociation	1
	Insomnia	1
Renal and urinary disorders	Urinary retention	1
Reproductive system and breast disorders	Menstrual disorder	1
	Menstruation delayed	1
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1
	Nasal congestion	1
	Oropharyngeal pain	1
	Wheezing	1
Skin and subcutaneous tissue disorders	Acne	1
	Alopecia	3
	Alopecia areata	1
	Dry skin	1
	Erythema	1
	Erythema multiforme	1
	Henoch-schonlein purpura	1
	Hyperhidrosis	1
	Hypoaesthesia facial	1
	Livedo reticularis	2
	Petechiae	1
	Photosensitivity reaction	2
	Purpura	2
	Rash	4
	Rash erythematous	1
	Skin disorder	1
	Urticaria	1
	Vitiligo	1
Vascular disorders	Pallor	2
	Peripheral coldness	3
Total reactions		**207**
Total reports		**73**

ANNEXE 4

Swine Flu (H1N1) Vaccines – Celvapan and Pandemrix
UK Suspected Adverse Reaction Analysis

Safeguarding public health

FINAL PUBLIC SUMMARY

UK Suspected Adverse Reaction Analysis

Swine Flu (H1N1) Vaccines – Celvapan and Pandemrix

26 March 2010

This final public summary provides an overview of all UK reports of suspected adverse reactions to the new swine flu (H1N1) vaccines (Celvapan and Pandemrix) received by MHRA between Monday 15th October 2009 and Tuesday 16th March 2010 (inclusive)[1]. These reports have been voluntarily submitted to MHRA by UK healthcare professionals and members of the public via the MHRA's 'Swine Flu ADR Portal' (www.mhra.gov.uk/swineflu) and the Yellow Card Scheme. It also includes all UK reports submitted by the Marketing Authorisation holders for Celvapan (Baxter) and Pandemrix (GSK) as part of their legal requirements.

The suspected adverse reactions listed in the attached Vaccine Analysis Prints have been coded using 'MedDRA' terminology[2].

It is important to note that a report of a reaction does not necessarily mean that it has been caused by the vaccine in question. We encourage reporters to report *suspected* adverse reactions i.e. the reporter does not have to be sure that the vaccine caused the reaction – a mere suspicion will suffice. Therefore, reports submitted to MHRA may be true adverse effects of the vaccine, psychogenic reactions related to the process of vaccination rather than to the specific vaccine itself (e.g. nervousness or anxiety about needles or vaccination); or they may be purely coincidental events that would have occurred anyway in the absence of vaccination (e.g. events due to underlying medical conditions). For this reason **this summary is not a list of known or proven adverse reactions to H1N1 vaccines and must not be interpreted and used as such.** A list of the recognised adverse effects of Celvapan and Pandemrix is provided in the product information for healthcare professionals (Summary of Product Characteristics) and patients (Patient Information Leaflet), copies of which are available on our website (www.mhra.gov.uk/swineflu).

Suspected adverse reaction reporting rates are highly variable and are dependent on many factors. Therefore these data cannot be used to determine the frequency of occurrence of adverse reactions to the H1N1 vaccines. Furthermore, the use of the two H1N1 vaccines available in the UK is expected to differ considerably in terms of the level of exposure and patient populations exposed (most will receive the Pandemrix brand). For these reasons **the data included in this report can not be used to directly compare the relative safety of Pandemrix and Celvapan.**

All reports of suspected adverse reactions to Celvapan and Pandemrix are closely monitored by a dedicated team of safety specialists at the MHRA.

[1] Suspected ADR data are released with a 1 week delay in order to ensure that MHRA has time to validate, extract and assess the data before publication.

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

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Headline summary:

1. Up to and including Tuesday 16th March 2010, MHRA has received a total of 3,310 UK reports of suspected adverse reactions to the H1N1 vaccines which include a total of 8,608 suspected reactions (a single report may contain more than one reaction). The latest figures indicate that more than 5 million people have now been vaccinated in the UK and at least 49.9 million doses of H1N1 vaccines, including at least 28.9 million doses of Pandemrix and 659,000 doses of Celvapan, have now been administered across Europe.

2. Reports of suspected adverse reactions to Pandemrix make up 86% (n=2,843) of all reports received in the UK for H1N1 vaccines. This is not unexpected given the *presumed*[1] difference in the extent of use of the two vaccines. The vaccine brand was not reported in 13% (n=430) of reports.

3. **The total number of reports and the nature of suspected adverse reactions reported so are as expected.** The most frequently reported suspected adverse reactions are injection site reactions (e.g. pain, swelling, redness) or other generalised symptoms such as nausea, vomiting, dizziness muscle pain, fever, fatigue, headache and swollen glands. Generally these were not serious and short-lived.

4. Twenty-three deaths following H1N1 swine flu vaccination have been reported in the UK to date (total excludes foetal/neonatal deaths following *in-utero exposure*). There is currently no suggestion that the vaccine contributed to any of these deaths. All reports of death following vaccination with H1N1 vaccines will be kept under close review.

5. Seven cases of intra-uterine death/still birth, two cases of neonatal death and twenty-six reports of spontaneous abortion have been reported for H1N1 vaccines in the UK. Across Europe, it is estimated that more than 448,000[4] pregnant women have been vaccinated with H1N1 vaccines, including at least 159,000 in the UK. Analysis of the available data, including data from Europe, indicates that the number of cases of adverse pregnancy outcomes reported to date does not exceed what would be expected based on normal background rates. There is no evidence of any H1N1 vaccine-associated risk to pregnancy.

6. Ten cases of *suspected* Guillain Barre Syndrome (GBS) have been reported in the UK to date. Further information is awaited in order to assess diagnostic certainty. **There is currently no evidence across Europe that H1N1 vaccines cause GBS or other similar neurological conditions.**

7. More than 650,000 healthy children aged less than 5-years have been vaccinated in the UK to date (including healthy children). The safety profile of one dose of the vaccine in children is broadly consistent with that for adults.

8. Further information on the type of suspected adverse reactions reported for the H1N1 vaccines is provided in **Annex 1**.

9. No unexpected new safety issues have been identified from reports received to date. **The balance of benefits and risks for Celvapan and Pandemrix remains positive.**

10. If identified, information on new and emerging safety signals will be provided in this report together with details of any resulting regulatory action or changes to prescribing advice deemed necessary.

1. VACCINE EXPOSURE DATA

At least 49.9 million doses of H1N1 vaccines have now been administered across Europe, including at least 28.9 million doses of Pandemrix and 659,000 doses of Celvapan[3]. The latest figures from the Department of Health suggest that at least 5 million people have now been vaccinated in England (as of 18 March 2010)[4].

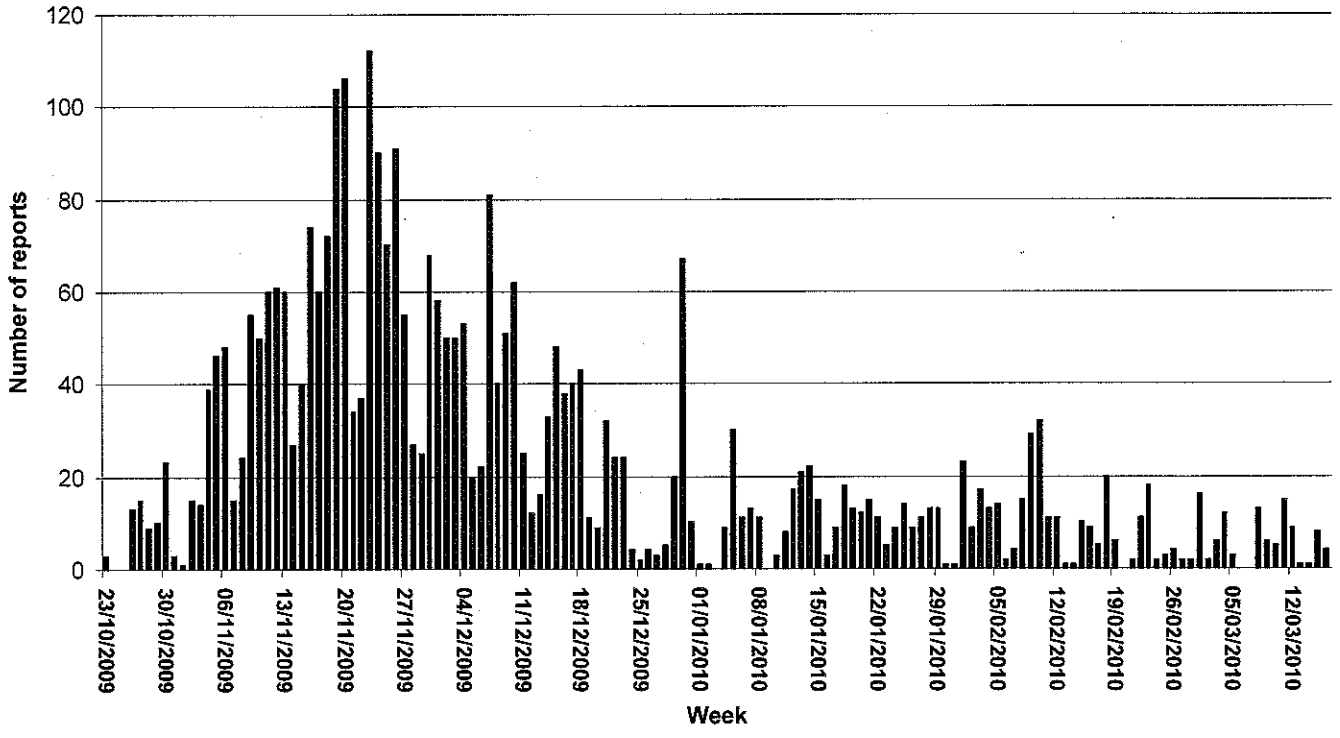
2. ADVERSE REACTION REPORTING TRENDS

Up to and including Tuesday 16th March 2010, the MHRA has received a total of 3,310 UK reports of suspected ADRs to the H1N1 vaccines which include a total of 8,608 suspected reactions (a single report may contain more than one reaction).

Chart 1 below outlines the number of reports of suspected adverse reactions to H1N1 vaccines received on a daily basis since receipt of the first report on 23 October 2009. Over the past 2-3 months the number of reports received has fallen in line with the decrease in the number of people vaccinated in the UK.

Chart 1

Number of reports of suspected adverse reactions reported via the MHRA Swine Flu ADR Portal per day for H1N1 vaccines

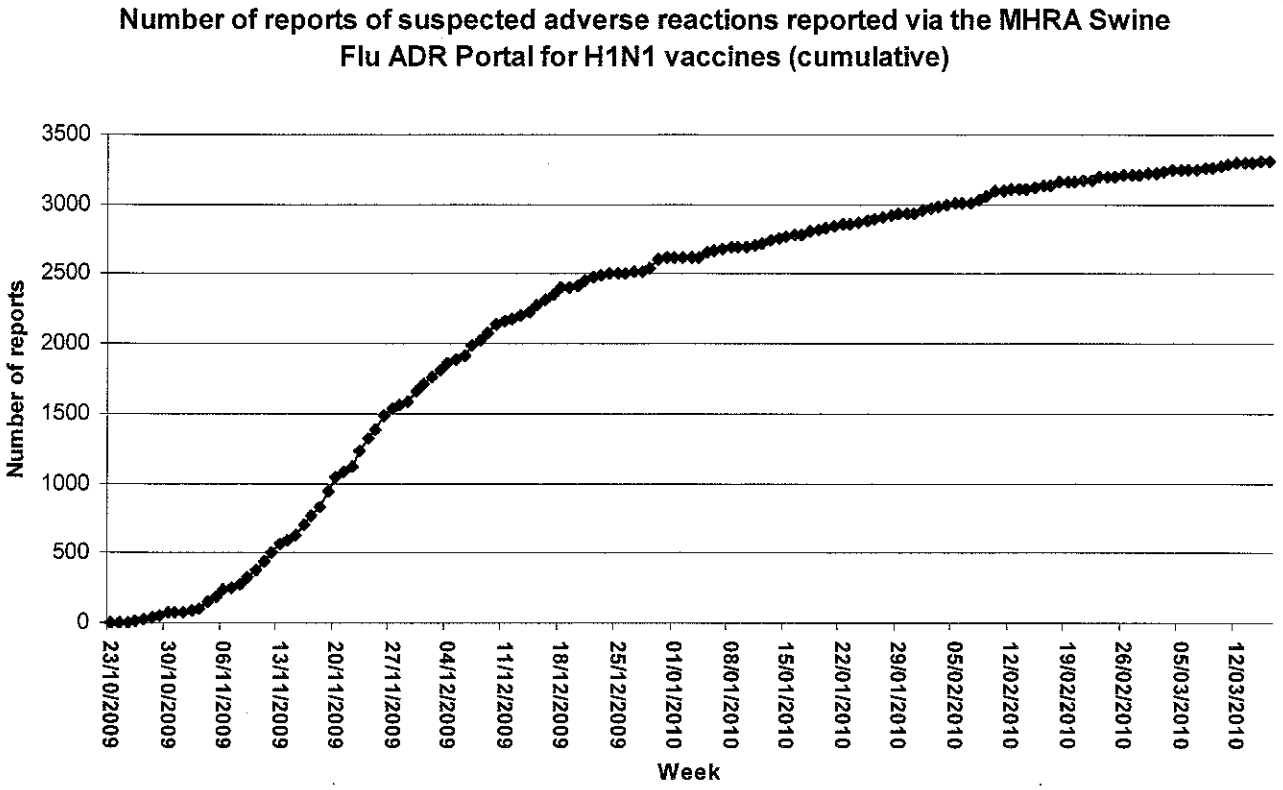


[3] Chief Medical Officer's fortnightly briefing (18 March 2010): http://www.dh.gov.uk/dr_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_114261.pdf

[4] Fourteenth Pandemic Update from European Medicines Agency (24 March 2010): http://www.ema.europa.eu/pdfs/influenza/19045210en.pdf

Chart 2 below shows how the number of UK reports of suspected adverse reaction to H1N1 vaccines (all brands) has increased since the start of the H1N1 vaccination programme.

Chart 2



2.1 Reports by Vaccine Brand

The majority of reports of suspected adverse reactions to swine flu vaccines received in the UK to date are for Pandemrix (86%). The vaccine brand was not reported in 13% of reports. The distribution of reports between Celvapan and Pandemrix is not unexpected given the presumed likely difference in the extent of use of the two vaccines in the UK[5]. In line with this, the majority of reports in which the vaccine brand is unknown are likely to relate to Pandemrix given the presumed difference in extent of use of the two vaccines.

Table 1. Reports by Vaccine Brand

	Total Reports	Total Suspected Adverse Reactions	Number of Fatal Suspected Adverse Reactions
Celvapan	37 (1%)	82	0
Pandemrix	2843 (86%)	7314	29*
Brand unknown	430 (13%)	1212	4$
Total	**3310**	**8608**	**33**

* Total number of fatal cases includes 3 cases of intra-uterine death and 2 cases of stillbirth following *in utero* exposure
$ Total number of fatal cases includes 2 cases of intra-uterine death following *in utero* exposure

Further information on the types of suspected adverse reactions reported for H1N1 vaccines is provided in **Annex 1** and in **Section 3** below.

[5] Detailed exposure data by vaccine brand is not available to us.

3. ANALYSIS OF SUSPECTED ADVERSE REACTIONS REPORTED

The most frequently reported suspected reactions are injection site reactions (including pain, swelling, numbness and bruising) and symptoms such as dizziness, paraesthesia (pins and needles, skin tingling), flu-like illness[6], headache, fatigue, muscle aches, fever, lymphadenopathy (swollen glands), nausea and vomiting which are recognised and common effects of many vaccines, including the swine flu vaccines.

3.1 Suspected Adverse Reactions with a Fatal Outcome

People with serious, chronic illness are more likely to die compared to fit and healthy people. This is because many people with serious illness may die as a result of a natural progression of their underlying medical condition (e.g. cancer, heart disease, lung disease, neurological disease) or because they develop other serious and life-threatening acute illnesses to which they are more susceptible because of their underlying medical condition. People with chronic serious illnesses are more susceptible to the serious complications of swine flu (which may include death) and are therefore being vaccinated as a priority.

Given that most people vaccinated in the UK to date have had serious, chronic pre-existing medical conditions it is not unexpected that some of these people may experience a progression or worsening of their condition and die shortly after being vaccinated. For reasons outlined above, it is important to bear in mind that these are likely to be purely coincidental events and would have occurred anyway in the absence of vaccination. Also, although the death may have occurred shortly after receiving the vaccine, this does not in itself mean that the vaccine was responsible for the death.

MHRA has received thirty-two UK reports of suspected adverse reactions to swine flu vaccines in which the patient died. This total includes seven reports of foetal death/stillbirth and 2 neonatal deaths following exposure to the vaccine during pregnancy. These nine reports are considered separately in section 3.2.1 below.

The remaining twenty-three cases concerned twenty-one adults (median age: 72 years) and two children. All had significant pre-existing medical conditions that could provide an explanation for the deaths. All reports of fatal events are reviewed carefully, and in detail, by MHRA. **There is no suggestion that the H1N1 vaccines contributed to any of these deaths.**

3.2 Suspected Adverse Reactions in Special Populations

3.2.1 Pregnant women

Pregnant women are at an increased risk of developing severe illness due to swine flu complications and are being offered the swine flu vaccine as one of the Government's priority groups. At least 159,000 pregnant women have been vaccinated with H1N1 vaccines in England.

We have received a total of 120 reports of suspected adverse reactions to H1N1 vaccines in pregnant women.

[6] The H1N1 swine flu vaccines do not contain live virus and therefore can not cause influenza.

3.2.1.1 The pregnant woman

More than a half of suspected adverse reactions reported following vaccination during pregnancy involve reactions for the pregnant woman only, with no reported adverse effects to the pregnancy. These cases mostly reported non-serious and recognised side effects of H1N1 vaccines such as injection site reactions and flu-like illness, and these are consistent with the observed safety profile of the vaccines in the general adult population.

Two cases of particular interest have been reported; one case of Guillain Barre Syndrome and one case of HELLP syndrome (vaccine brand is unknown in both cases). The case of GBS is discussed further in section 3.3.1 below.

In the case of HELLP syndrome the foetus died at 24 weeks gestation but the woman recovered. HELLP syndrome is a collection of symptoms that occurs in pregnant women who have pre-eclampsia or eclampsia who also suffer liver damage and abnormalities in blood clotting. It is characterised by **H**aemolysis, **El**evated liver enzymes and a **L**ow **P**latelet count. It is thought to occur in 0.5 to 0.9% of all pregnancies and in 10-20% of cases with severe pre-eclampsia. Up to 25% of women may develop serious complications if HELLP is not treated early and there is significant mortality if left untreated. The mortality rate among babies born to mothers with HELLP syndrome varies and depends mainly on gestation and birth weight. More than 145,000 pregnant women have received H1N1 vaccines in the UK and this single case report of HELLP syndrome does not raise any concern about any vaccine-related risks to pregnant women. Given the background incidence of HELLP syndrome in pregnant women, this single case does not exceed the number of cases that would be expected to occur in unvaccinated pregnant women.

No vaccine-related risks to pregnancy have been identified.

3.2.1.2 Adverse effect to the foetus or on pregnancy outcome

Table 5 below lists the adverse effects to the foetus or pregnancy outcome reported following H1N1 vaccination in pregnant women in the UK. The events are listed in order of frequency and in cases where one or more pregnancy-related event was reported, the most serious term was selected to prevent double counting of cases.

Table 5

Adverse pregnancy outcome	Number of Cases
Spontaneous abortion*	26
Intra-uterine death	5
Premature labour	3
Stillbirth	2
Reduced foetal movements	2
Neonatal death	2
Congenital hip deformity	1
Threatened labour	1
Total	**42**

* Spontaneous abortion (<24 weeks gestation); intra-uterine death/stillbirth (>24 weeks gestation).

Given that the background rate of foetal death/stillbirth in the UK is estimated to be around 5 stillbirths per 1000 pregnancies and that at least 159,000 pregnant women have been vaccinated in England to date, the seven reported cases do not raise any vaccine safety concerns. The number of cases of stillbirth/intra-uterine death following vaccination reported to date does not exceed the number of cases that would be expected in the absence of vaccination.

Spontaneous abortion is not uncommon in early pregnancy – data suggest that 20 -25% of women who become pregnant will suffer a spontaneous abortion and that the risk is greatest during the first trimester. The number of cases of spontaneous abortion reported to date for H1N1 vaccines does not exceed what would be expected given the background rate of spontaneous abortion in the UK.

Inevitably foetal death/stillbirth and spontaneous abortion may occur coincidentally following vaccination without the vaccine playing any causal role in the event. Other factors such as obstetric history, underlying medical conditions, and exposure to chemicals, smoking status and alcohol use can all influence the risk of these events.

The other adverse pregnancy outcome reported for H1N1 vaccines to date are also relatively common events and the number of cases reported is consistent with these being co-incidental events that would have occurred anyway in the absence of vaccination.

There is no evidence to suggest that the H1N1 vaccines carry any risks to pregnancy or the unborn baby.

As with all suspected adverse reactions, MHRA continues to keep under close review all reports of suspected adverse effects following vaccination during pregnancy.

3.2.2 Children

More than 650,000 doses of H1N1 vaccines have been administered to healthy children aged less than 5-years in England to date (up to 14th March 2010). The safety profile of the vaccines in children is broadly consistent with that for seen for adults.

We have received a total of 440 reports of suspected adverse reactions to swine flu vaccines in children aged less than 16 years. In four of these cases the child was reported to have died. Two children had significant underlying medical conditions and the two remaining cases are the two cases of neonatal death mentioned in section 3.2.1 above. There is no indication that the vaccine contributed to these deaths.

The majority of the reported suspected reactions in children are non-serious, recognised side effects of many vaccines including the swine flu vaccines, or can be attributed to the process of vaccination rather than the vaccine itself. These reactions include injection site reactions, flu-like illness, muscle aches and pains, rash, headache, dizziness, nausea, vomiting, diarrhoea and psychogenic reactions including faints.

3.3 Adverse Events of Special Interest (AESIs)

3.3.1 Guillain Barre Syndrome (n=10)

Ten cases of suspected Guillain Barre Syndrome (GBS) have been reported in the UK for H1N1 vaccines to date (7 for Pandemrix; 1 for Celvapan; 2 brand unknown). Two cases involved young children and one case involved a pregnant woman. Based on the information currently available, only two of the cases described so far meet the Brighton Collaboration[7] case definition for GBS.

GBS can occur following infections and it can also develop spontaneously without any obvious cause. During the winter period, when viruses and other pathogens that can cause GBS are widely circulating, it is inevitable that cases of GBS will occur by coincidence not long after vaccination, without the vaccine playing a role.

MHRA has in place a real-time statistical analysis of the observed (reported) number of cases of AESIs, such as GBS, compared to the expected background incidence amongst the number of vaccinees. This includes an adjustment for likely under-reporting of cases. The total number of suspected cases of GBS reported in the UK (and Europe) following vaccination does not exceed the number of cases that would be expected in the normal background population (i.e. in the absence of vaccination) suggesting that these cases were probably coincidental events.

There is currently no evidence to confirm that the H1N1 swine flu vaccines cause Guillain Barre Syndrome. This is being kept under close review.

3.3.2 Myasthenia gravis

Two cases of myasthenia gravis (MG) have been reported in the UK to date. However, further information received for one of these cases states that the diagnosis of MG (and GBS) has been excluded. The patient experienced transient muscular or neurological problems that were considered to be consistent with the transient, mild to moderate recognised effects of the vaccine. The information concerning the second reported case is not sufficient to confirm the diagnosis of MG and further information has been requested.

[7] www.brightoncollaboration.org

The MHRA has, in addition received a single report of relapse of ocular MG. MHRA is unaware of any other cases of MG reported within Europe in association with swine flu vaccines.

As part of MHRA's real-time statistical analyses implemented for swine flu vaccine safety monitoring, we have calculated the expected background incidence of MG amongst the 5 million or so people vaccinated so far in the UK. This indicates that we would expect to see 8 to 9 co-incidental cases of MG within 6 weeks of vaccination amongst those vaccinated, without the vaccine having played any role.

There is no evidence that the H1N1 swine flu vaccines cause myasthenia gravis.

3.3.3 Multiple sclerosis

One case of multiple sclerosis aggravated has been reported in the UK to date. Given the number of people vaccinated in the UK to date and that MS is one of the priority groups for swine flu vaccination, this single case report of exacerbated MS does not suggest a causal association between swine flu vaccines and exacerbation of MS.

3.3.4 Convulsions

Thirty-nine cases of seizure disorders have been reported for H1N1 vaccines in the UK. Several of these cases occurred in vaccinees with pre-existing epilepsy or seizure disorder.

Two cases of convulsions in adults with a history of epilepsy (one poorly controlled) had a fatal utcome. It is recognised that some people with epilepsy may die suddenly with no other cause found. It is an uncommon but widely recognised syndrome called Sudden Unexpected Death in Epilepsy (SUDEP). It can occur in people with infrequent as well as severe epilepsy. There is currently no evidence to indicate that the vaccine contributed to these fatal events.

A number of cases involved children aged less than 15-years and the majority of these were febrile convulsions (i.e. convulsions occurring as a result of a sharp rise in body temperature/fever). Febrile convulsions are a potential rare side effect of Pandemrix and the Pandemrix product information has been updated to include a warning about the high rates of fever in children with the second dose of Pandemrix and that this may lead to febrile convulsions.

MHRA continues to monitor closely all reports of convulsions.

3.3.5 Other Nervous System Disorders

The reports of paraesthesia (mainly reported as pins and needles and skin tingling), sensory disturbance and hypoaesthesia ('numbness') were generally transient and localised to the injection site or to the injected limb. A smaller number of cases of generalised paraesthesia have been reported. In most cases this was transient. Paraesthesia is a recognised side-effect of Pandemrix and is listed in the product information as such.

Reports of neuralgia (n=8) and facial neuralgia (n=4) were generally localised to the face and/or injected limb and were transient and not associated with any serious neurological outcome.

Two cases of nerve injury have been reported to date. One of these cases appears to be related to the injection technique and is associated with sensory loss with pins and needles along the ulnar distribution of the vaccinated arm. The second was associated with dizziness and head pressure and the term 'nerve damage' seems to have been selected to describe an anxiety 'nervous' state rather than true nerve damage.

MHRA has received one case of transverse myelitis which contains little information. Further information has been requested. One case of encephalopathy has been reported in the UK. The encephalopathy developed 4 days post vaccination and at the time of reporting, was recovering well spontaneously. Further information has been requested.

Cases of paralysis (n=7), hemiplegia (n=1), hemiparesis (n=1), monoplegia (n=3) and diplegia (n=1) have been reported in the UK for H1N1 vaccines. These were short-lasting events and are not indicative of actual paralysis or any serious neurological/neuromotor disturbance. Several cases were reported as 'inability to

move limb' (translated in our database medical dictionary to 'paralysis'). Our initial assessment is that these cases most likely represent impaired mobility of the injected limb probably due to pain and stiffness rather than a paralysis of neurological origin and this has been confirmed as the case in a number of these cases following receipt of further information. The single case of polyneuropathy was described as pins and needles and numbness in the injected arm.

The cases of trigeminal nerve paresis (n=1), facial paresis (n=1) and facial palsy (n=7) have been fully evaluated and the short time to onset in these cases would suggest that these are coincidental events and are not related to the vaccine. This is supported by MHRA's analysis showing that the number of cases reported in the UK (and across Europe) does not exceed the expected background rate of facial palsy amongst vaccinees.

More than 49.9 million doses of H1N1 vaccines have now been given across Europe and there is no evidence that these vaccines cause GBS or similar neurological disorders.

3.3.2 Symptoms of serious allergic or anaphylactic reactions

There have been several reports of allergic reactions reported for H1N1 vaccines. For many of the reports of anaphylaxis, the available clinical information does not allow diagnosis to be confirmed. However, where clinical information is available, this suggests that the allergic reaction was less severe than a true anaphylactic reaction in several of these cases.

Anaphylaxis is a known, although very rare, risk with any vaccine and is thought to occur at a frequency of between one and ten cases per million doses of vaccine given. The prescribing information for H1N1 swine flu vaccines warn of this possible risk and the need to ensure that appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event.

At least 49.9 million doses of H1N1 vaccines have now been given across Europe and there is currently no evidence to suggest that there is a greater risk of anaphylaxis with Pandemrix or any other H1N1 swine flu vaccine, or that these cause more severe cases, than we would normally expect.

4. OVERALL CONCLUSIONS

The vast majority of reports of suspected adverse reactions to H1N1 vaccines received to date are for Pandemrix. This is not unexpected given the presumed[3] greater usage of Pandemrix in the UK to date.

The total number and the nature of suspected adverse reactions reported are very much as expected. The most frequently reported suspected adverse reactions are injection site reactions (e.g. pain, swelling, redness) or other generalised symptoms such as nausea, vomiting, dizziness muscle pain, fever, fatigue, headache and swollen glands. In general, these are not serious and are short lasting. For the isolated cases of other medical conditions reported, the available evidence does not suggest that the vaccine caused the condition and these may have been coincidental events.

There is no indication at present that the vaccines have contributed to any of the reported cases of death and there is no evidence of any risks to pregnancy.

No unexpected new safety issues have been identified from UK data to date. We continue to keep a number of issues under close review.

The benefit – risk balance for Celvapan and Pandemrix remain positive.

ANNEX 1

Line-listing of all suspected adverse reactions reported via the MHRA Swine Flu ADR Portal for H1N1 vaccines (data up to 16th March 2010)

Vaccine Analysis Print - Swine Flu Vaccines

Run Date: Unspecified to 16 March 2010		
Total number of reactions: 8608	**Total number of ADR reports:** 3310	**Total number of fatal ADR reports:** 32

System Organ Class	Reactions	Fatal Reactions
Blood and lymphatic system disorders	98	1
Cardiac disorders	65	2
Congenital, familial and genetic disorders	1	0
Ear and labyrinth disorders	49	0
Eye disorders	106	0
Gastrointestinal disorders	1002	0
General disorders and administration site conditions	2680	8
Hepatobiliary disorders	4	0
Immune system disorders	51	0
Infections and infestations	172	3
Injury, poisoning and procedural complications	48	0
Investigations	199	0
Metabolism and nutrition disorders	56	0
Musculoskeletal and connective tissue disorders	1245	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0
Nervous system disorders	1465	4
Pregnancy, puerperium and perinatal conditions	45	7
Psychiatric disorders	185	0
Renal and urinary disorders	19	0
Reproductive system and breast disorders	13	0
Respiratory, thoracic and mediastinal disorders	421	3
Skin and subcutaneous tissue disorders	572	1
Social circumstances	7	0
Surgical and medical procedures	2	0
Vascular disorders	95	1
Total	8608	32

Glossary/Abbreviations

ADR - Adverse Drug Reaction

Age group - lists which age groups are included in the Drug Analysis Print - either ALL, Adolescent, Adult, Child, Elderly, Infant or Neonate

Data lock date - shows data on the database at this specified date and time

HLT - High Level Term - see definition of MedDRA

MEDRA - this stands for Medical Dictionary for Regulatory Activities, which is the internationally agreed list of terms used for Medicines Regulation. MedDRA groups related adverse drug reaction terms in a hierarchical structure whereby the 'preferred term' (PT) (e.g. tunnel vision) is grouped under the broader heading the 'high level term' (HLT) (e.g. visual field disorders). 'High level terms' are contained within the 'system organ class' (SOC) (e.g. eye disorders). The 'preferred term' is the most specific term on the Drug Analysis Print, while the 'system organ class' is the most general

Multi active constituent products - contain the drug constituent of interest plus one or more other drug constituents (e.g. co-codamol contains paracetamol and codeine)

NEC - appears in MedDRA and stands for Not Elsewhere Classified

NOS - appears in MedDRA and stands for Not Otherwise Specified

PBG - Product Brand Generic - this means drug brand name e.g. Amoxil is a PBG for the drug substance amoxicillin

Products included in this print - this is a list of the products for which at least one suspected Adverse Drug Reaction (ADR) report has been received that specifies that product as a 'suspected drug' (i.e. suspected causal association with the reaction). It does not provide an exhaustive list of the products which contain the named drug substance

PT - Preferred Term - see definition of MedDRA

Reaction - defines which ADRs are included in the Drug Analysis Print - either ALL, Serious or Non-Serious

Reporter type - lists the reporter types which are included in the Drug Analysis Print - either Patient, Health Professional or ALL (i.e. both)

Report run date - the date the Drug Analysis Print was produced

Route of admin - lists the route of administration of the suspect drug for which reports are included in the Drug Analysis Print, e.g. ORAL only includes reports where the suspect drug was specified as having been taken by the oral route, or ALL which includes all routes of administration

Spontaneous - suspected ADR reports sent in to the Yellow Card Scheme are called spontaneous reports

Single active constituent products - contain only the drug substance of interest

System Organ Class (SOC) - this is the highest level in MedDRA which groups together reactions that affect similar systems/organs in the body

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Blood and lymphatic system disorders		
Anaemias haemolytic immune		
Anaemia haemolytic autoimmune	1	0
Anaemias NEC		
Anaemia	2	0
Haematological disorders		
Methaemoglobinaemia	1	0
Haemolyses NEC		
Lymphatic system disorders NEC		
Lymph node pain	3	0
Lymphadenitis	3	0
Lymphadenopathy	72	0
Marrow depression and hypoplastic anaemias		
Pancytopenia	1	1
Neutropenias		
Neutropenia	1	0
Spleen disorders		
Splenomegaly	1	0
Thrombocytopenias		
Idiopathic thrombocytopenic purpura	8	0
Thrombocytopenia	4	0
Autoimmune thrombocytopenia	1	0
Blood and lymphatic system disorders SOC Total	98	1

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Cardiac disorders		
Cardiac signs and symptoms NEC		
Cyanosis	1	0
Palpitations	32	0
Ischaemic coronary artery disorders		
Angina pectoris	2	0
Myocardial infarction	3	2
Heart failures NEC		
Cardiac failure congestive	1	0
Noninfectious pericarditis		
Pericarditis	1	0
Rate and rhythm disorders NEC		
Bradycardia	2	0
Extrasystoles	1	0
Tachycardia	15	0
Supraventricular arrhythmias		
Atrial fibrillation	3	0
Sinus tachycardia	2	0
Supraventricular tachycardia	1	0
Ventricular arrhythmias and cardiac arrest		
Cardiac arrest	1	0
Cardiac disorders SOC Total	65	2

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Congenital, familial and genetic disorders		
Musculoskeletal and connective tissue disorders of limbs congenital		
Congenital hip deformity	1	0
Congenital, familial and genetic disorders SOC Total	**1**	**0**

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Ear and labyrinth disorders		
Hearing losses		
Deafness	2	0
Deafness neurosensory	2	0
Inner ear signs and symptoms		
Tinnitus	13	0
Vertigo	13	0
Vertigo positional	1	0
Inner ear disorders NEC		
Meniere's disease	1	0
Inner ear disorder	2	0
Ear disorders NEC		
Ear pain	15	0
Ear and labyrinth disorders SOC Total	49	0

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Eye disorders		
Blindness (excl colour blindness)		
Blindness transient	1	0
Conjunctival infections, irritations and inflammations		
Conjunctivitis	5	0
Eyelid movement disorders		
Blepharospasm	2	0
Eyelid ptosis	1	0
Glaucomas (excl congenital)		
Ocular hypertension	1	0
Lacrimal disorders		
Dry eye	2	0
Lacrimation increased	2	0
Lid, lash and lacrimal infections, irritations and inflammations		
Blepharitis allergic	1	0
Eyelid oedema	5	0
Ocular disorders NEC		
Eye disorder	1	0
Eye pain	22	0
Eye swelling	7	0
Eyelid pain	1	0
Eyelid disorder	1	0
Ocular infections, inflammations and associated manifestations		
Eye discharge	2	0
Eye irritation	3	0
Ocular hyperaemia	2	0
Eye pruritus	1	0
Ocular nerve and muscle disorders		
Ocular myasthenia	1	0
Eye movement disorder	1	0
Ocular sensation disorders		
Abnormal sensation in eye	1	0
Asthenopia	3	0
Eye rolling	2	0

Photophobia	6	0
Partial vision loss		
Visual acuity reduced	1	0
Visual acuity reduced transiently	1	0
Pupil disorders		
Mydriasis	2	0
Visual disorders NEC		
Diplopia	2	0
Photopsia	1	0
Scintillating scotoma	1	0
Vision blurred	18	0
Visual impairment	6	0
Eye disorders SOC Total	106	0

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Gastrointestinal disorders		
Diarrhoea (excl infective)		
Diarrhoea	176	0
Diarrhoea haemorrhagic	3	0
Dyspeptic signs and symptoms		
Dyspepsia	7	0
Faecal abnormalities NEC		
Mucous stools	1	0
Flatulence, bloating and distension		
Abdominal distension	1	0
Flatulence	2	0
Gastritis (excl infective)		
Gastritis	1	0
Gastrointestinal and abdominal pains (excl oral and throat)		
Abdominal pain	47	0
Abdominal pain lower	5	0
Abdominal pain upper	67	0
Gastrointestinal atonic and hypomotility disorders NEC		
Constipation	3	0
Gastrooesophageal reflux disease	1	0
Gastrointestinal disorders NEC		
Gastrointestinal disorder	1	0
Gastrointestinal dyskinetic disorders		
Gastrointestinal motility disorder	1	0
Non-site specific gastrointestinal haemorrhages		
Haematemesis	1	0
Haematochezia	1	0
Gingival disorders NEC		
Gingivitis	1	0
Gingival pains		
Gingival pain	1	0
Intestinal haemorrhages		
Rectal haemorrhage	1	0
Gastrointestinal signs and symptoms NEC		

Abdominal discomfort	6	0
Breath odour	1	0
Dysphagia	2	0
Faecal incontinence	1	0
Stomach discomfort	7	0
Nausea and vomiting symptoms		
Nausea	311	0
Retching	1	0
Vomiting	236	0
Vomiting in pregnancy	5	0
Vomiting projectile	3	0
Regurgitation	1	0
Oral dryness and saliva altered		
Dry mouth	14	0
Lip dry	1	0
Saliva altered	1	0
Oral soft tissue disorders NEC		
Lip swelling	16	0
Chapped lips	1	0
Lip blister	2	0
Oral soft tissue pain and paraesthesia		
Oral pain	2	0
Paraesthesia oral	22	0
Oral soft tissue swelling and oedema		
Oedema mouth	2	0
Oral soft tissue signs and symptoms		
Oral discomfort	1	0
Oral pruritus	1	0
Hypoaesthesia oral	11	0
Acute and chronic pancreatitis		
Pancreatitis	1	0
Pancreatitis acute	1	0
Salivary gland disorders NEC		
Salivary gland pain	1	0
Stomatitis and ulceration		
Mouth ulceration	7	0
Stomatitis	2	0
Tongue disorders		
Glossitis	1	0
Tongue disorder	2	0
Tongue ulceration	1	0

Tongue signs and symptoms		
Swollen tongue	7	0
Tongue coated	1	0
Tongue discolouration	1	0
Tongue oedema	2	0
Tongue dry	1	0
Dental pain and sensation disorders		
Toothache	4	0
Oesophagitis (excl infective)		
Oesophagitis	1	0
Gastrointestinal disorders SOC Total	1002	0

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
General disorders and administration site conditions		
Application and instillation site reactions		
Application site erythema	1	0
Application site pain	30	0
Application site pruritus	6	0
Application site rash	1	0
Application site reaction	2	0
Application site warmth	2	0
Application site swelling	1	0
Application site haematoma	3	0
Asthenic conditions		
Asthenia	52	0
Fatigue	266	0
Malaise	173	0
Body temperature altered		
Temperature regulation disorder	1	0
Death and sudden death		
Death	3	3
Death neonatal	2	2
Sudden death	3	3
Febrile disorders		
Pyrexia	462	0
Gait disturbances		
Gait disturbance	8	0
Loss of control of legs	2	0
Abasia	1	0
General signs and symptoms NEC		
Condition aggravated	1	0
Influenza like illness	260	0
Irritability	4	0
Local reaction	60	0
Local swelling	12	0
Multi-organ failure	1	0
Swelling	51	0

Induration	2	0
Foaming at mouth	1	0
Inflammations		
Inflammation	3	0
Injection and infusion site reactions		
Injection site anaesthesia	1	0
Injection site cyst	1	0
Injection site erythema	46	0
Injection site haematoma	13	0
Injection site hypersensitivity	1	0
Injection site induration	9	0
Injection site inflammation	103	0
Injection site irritation	16	0
Injection site mass	11	0
Injection site oedema	12	0
Injection site pain	149	0
Injection site paraesthesia	1	0
Injection site phlebitis	1	0
Injection site pruritus	15	0
Injection site rash	17	0
Injection site reaction	9	0
Injection site urticaria	3	0
Injection site vesicles	1	0
Injection site warmth	10	0
Injection site discolouration	3	0
Injection site swelling	82	0
Injection site discomfort	2	0
Injected limb mobility decreased	1	0
Injection site discharge	1	0
Mucosal findings abnormal		
Mucosal haemorrhage	1	0
Oedema NEC		
Face oedema	1	0
Oedema peripheral	237	0
Localised oedema	1	0
Pain and discomfort NEC		
Chest discomfort	46	0
Chest pain	31	0
Discomfort	2	0
Facial pain	2	0
Pain	143	0

Tenderness	16	0
Axillary pain	7	0
Non-cardiac chest pain	4	0
Administration site reactions NEC		
Venipuncture site swelling	1	0
Administration site pain	1	0
Infusion site reactions		
Infusion related reaction	2	0
Feelings and sensations NEC		
Chills	150	0
Feeling abnormal	21	0
Feeling cold	12	0
Feeling drunk	1	0
Feeling hot	41	0
Feeling jittery	2	0
Hangover	2	0
Peripheral coldness	15	0
Thirst	5	0
Feeling of body temperature change	14	0
General disorders and administration site conditions SOC Total	2680	8

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Hepatobiliary disorders		
Cholestasis and jaundice		
Jaundice	1	0
Hepatobiliary signs and symptoms		
Hepatic pain	2	0
Hepatocellular damage and hepatitis NEC		
Hepatitis acute	1	0
Hepatobiliary disorders SOC Total	4	0

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Immune system disorders		
Allergies to foods, food additives, drugs and other chemicals		
Allergy to vaccine	1	0
Anaphylactic responses		
Anaphylactic reaction	24	0
Anaphylactic shock	1	0
Anaphylactoid reaction	3	0
Allergic conditions NEC		
Hypersensitivity	17	0
Serum sickness	2	0
Type I hypersensitivity	1	0
Type IV hypersensitivity reaction	1	0
Immune and associated conditions NEC		
Immunodeficiency disorders NEC		
Immunosuppression	1	0
Immune system disorders SOC Total	51	0

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Infections and infestations		
Bacterial infections NEC		
Cellulitis	21	0
Intestinal gangrene	1	1
Bacterial infection	1	0
Pneumonia bacterial	1	0
Conjunctivitis bacterial	1	0
Central nervous system and spinal infections		
Meningitis	1	0
Cryptococcal infections		
Gastroenteritis cryptococcal	1	0
Dental and oral soft tissue infections		
Parotitis	2	0
Tooth abscess	1	0
Tooth infection	1	0
Ear infections		
Ear infection	1	0
Otitis externa	1	0
Eye and eyelid infections		
Eye infection	1	0
Abdominal and gastrointestinal infections		
Diarrhoea infectious	1	0
Gastroenteritis	1	1
Haemophilus infections		
Haemophilus infection	1	0
Herpes viral infections		
Herpes zoster	5	0
Varicella	2	0
Oral herpes	2	0
Infections NEC		
Abscess	1	0
Infection	5	0
Injection site abscess	4	0
Injection site infection	2	0

Localised infection	2	0
Lymph gland infection	1	0
Respiratory tract infection	1	0
Inflammatory disorders following infection		
Kawasaki's disease	2	0
Influenza viral infections		
Influenza	17	0
Lower respiratory tract and lung infections		
Bronchitis	2	0
Bronchopneumonia	5	1
Lower respiratory tract infection	15	0
Pneumonia	3	0
Parainfluenzae viral infections		
Croup infectious	2	0
Male reproductive tract infections		
Orchitis	1	0
Sepsis, bacteraemia, viraemia and fungaemia NEC		
Sepsis	2	0
Skin structures and soft tissue infections		
Furuncle	2	0
Skin infection	1	0
Upper respiratory tract infections		
Laryngitis	1	0
Nasopharyngitis	29	0
Pharyngitis	1	0
Rhinitis	7	0
Sinusitis	2	0
Tracheitis	1	0
Upper respiratory tract infection	2	0
Urinary tract infections		
Cystitis	1	0
Kidney infection	2	0
Urinary tract infection	5	0
Viral infections NEC		
Encephalitis viral	1	0
Meningitis viral	1	0
Pneumonia viral	1	0
Sweating fever	3	0
Post viral fatigue syndrome	1	0
Infections and infestations SOC Total	172	3

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Injury, poisoning and procedural complications		
Anaesthetic complications		
Delayed recovery from anaesthesia	1	0
Gastrointestinal and hepatobiliary procedural complications		
Procedural nausea	1	0
Heat injuries (excl thermal burns)		
Heat oedema	1	0
Pregnancy related accidental exposures and injuries		
Drug exposure during pregnancy	8	0
Eye injuries NEC		
Retinal injury	1	0
Limb injuries NEC (incl traumatic amputation)		
Joint sprain	1	0
Skin injuries NEC		
Contusion	14	0
Muscle, tendon and ligament injuries		
Muscle strain	1	0
Neurological and psychiatric procedural complications		
Procedural dizziness	1	0
Non-site specific injuries NEC		
Fall	2	0
Non-site specific procedural complications		
Post procedural complication	1	0
Graft dysfunction	1	0
Overdoses		
Accidental overdose	1	0
Poisoning and toxicity		
Drug toxicity	1	0
Thermal burns		
Thermal burn	1	0
Nerve injuries NEC		
Nerve injury	2	0
Vaccination related complications		
Post vaccination syndrome	3	0

Vaccination complication	7	0
Injury, poisoning and procedural complications SOC Total	48	0

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Investigations		
Blood gas and acid base analyses		
Oxygen saturation decreased	1	0
Carbohydrate tolerance analyses (incl diabetes)		
Blood glucose abnormal	1	0
Blood glucose decreased	1	0
Blood glucose increased	6	0
Blood glucose fluctuation	1	0
Coagulation and bleeding analyses		
International normalised ratio increased	6	0
Liver function analyses		
Liver function test abnormal	1	0
Transaminases increased	1	0
Metabolism tests NEC		
Urine ketone body present	1	0
Physical examination procedures		
Body temperature	1	0
Body temperature decreased	3	0
Body temperature increased	132	0
Respiratory rate decreased	1	0
Respiratory rate increased	1	0
Weight decreased	6	0
Grip strength decreased	1	0
Body temperature fluctuation	1	0
Platelet analyses		
Platelet count decreased	1	0
Respiratory and pulmonary function diagnostic procedures		
Forced expiratory volume increased	2	0
Renal function analyses		
Blood creatinine increased	1	0
Skeletal and cardiac muscle analyses		
Blood creatine phosphokinase increased	1	0
Urinalysis NEC		
Blood urine present	2	0

Protein urine present	1	0
Vascular tests NEC (incl blood pressure)		
Blood pressure abnormal	2	0
Blood pressure decreased	6	0
Blood pressure increased	4	0
White blood cell analyses		
White blood cell count abnormal	1	0
Urinary tract function analyses NEC		
Urine output decreased	1	0
Heart rate and pulse investigations		
Heart rate increased	11	0
Heart rate irregular	1	0
Investigations SOC Total	199	0

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Metabolism and nutrition disorders		
Appetite disorders		
Anorexia	32	0
Decreased appetite	10	0
Hypophagia	1	0
Diabetes mellitus (incl subtypes)		
Gestational diabetes	1	0
Type 1 diabetes mellitus	2	0
General nutritional disorders NEC		
Hyperglycaemic conditions NEC		
Hyperglycaemia	2	0
Hypoglycaemic conditions NEC		
Hypoglycaemia	3	0
Total fluid volume decreased		
Dehydration	5	0
Metabolism and nutrition disorders SOC Total	56	0

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Musculoskeletal and connective tissue disorders		
Arthropathies NEC		
Arthritis	5	0
Arthritis reactive	4	0
Haemarthrosis	1	0
SLE arthritis	1	0
Bone related signs and symptoms		
Bone pain	2	0
Pain in jaw	1	0
Muscle infections and inflammations		
Myositis	4	0
Intervertebral disc disorders NEC		
Intervertebral disc protrusion	1	0
Joint related signs and symptoms		
Arthralgia	215	0
Joint stiffness	13	0
Joint swelling	8	1
Joint related disorders NEC		
Periarthritis	1	0
Musculoskeletal and connective tissue signs and symptoms NEC		
Posture abnormal	1	0
Sensation of heaviness	11	0
Mobility decreased	1	0
Musculoskeletal stiffness	59	0
Muscle pains		
Myalgia	288	0
Fibromyalgia	2	0
Muscle related signs and symptoms NEC		
Muscle spasms	18	0
Muscle twitching	5	0
Muscle fatigue	1	0
Muscle tightness	1	0
Muscle swelling	2	0
Muscle tone abnormalities		

Muscle rigidity	1	0
Floppy infant	1	0
Nuchal rigidity	2	0
Myopathies		
Rhabdomyolysis	2	1
Rheumatoid arthropathies		
Rheumatoid arthritis	3	0
Soft tissue disorders NEC		
Groin pain	3	0
Axillary mass	2	0
Tendon disorders		
Tendonitis	2	0
Tenosynovitis	2	0
Muscle weakness conditions		
Muscular weakness	30	0
Musculoskeletal and connective tissue pain and discomfort		
Back pain	45	0
Musculoskeletal pain	40	0
Neck pain	29	0
Pain in extremity	350	0
Musculoskeletal chest pain	2	0
Musculoskeletal discomfort	10	0
Limb discomfort	76	0
Musculoskeletal and connective tissue disorders SOC Total	1245	2

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Skin neoplasms benign		
Seborrhoeic keratosis	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC Total	1	0

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Nervous system disorders		
Acute polyneuropathies		
Guillain-Barre syndrome	10	0
Polyneuropathy	1	0
Central nervous system haemorrhages and cerebrovascular accidents		
Cerebral haemorrhage	2	2
Cerebrovascular accident	1	0
Haemorrhagic stroke	1	0
Cerebellar coordination and balance disturbances		
Coordination abnormal	1	0
Balance disorder	8	0
Disturbances in consciousness NEC		
Altered state of consciousness	1	0
Lethargy	93	0
Loss of consciousness	13	0
Sedation	1	0
Somnolence	37	0
Syncope	32	0
Dyskinesias and movement disorders NEC		
Dyskinesia	1	0
Hypokinesia	5	0
Psychomotor hyperactivity	3	0
Encephalitis NEC		
Encephalitis	1	0
Encephalopathies NEC		
Encephalopathy	2	0
Facial cranial nerve disorders		
Facial palsy	7	0
Facial paresis	1	0
Generalised tonic-clonic seizures		
Convulsion neonatal	1	0
Grand mal convulsion	7	0
Convulsion in childhood	1	0
Headaches NEC		

Headache	595	0
Sinus headache	7	0
Tension headache	9	0
Cluster headache	2	0
Memory loss (excl dementia)		
Amnesia	1	0
Memory impairment	1	0
Mental impairment (excl dementia and memory loss)		
Disturbance in attention	7	0
Migraine headaches		
Migraine	31	0
Migraine with aura	2	0
Migraine without aura	1	0
Myelitis (incl infective)		
Myelitis transverse	3	0
Narcolepsy and hypersomnia		
Hypersomnia	6	0
Neurological signs and symptoms NEC		
Dizziness	200	0
Dizziness postural	6	0
Fontanelle bulging	1	0
Head discomfort	9	0
Myoclonus	1	0
Presyncope	4	0
Unresponsive to stimuli	1	0
Neurological symptom	3	0
Neuromuscular disorders NEC		
Muscle contractions involuntary	4	0
Muscle spasticity	2	0
Neuromuscular junction dysfunction		
Myasthenia gravis	2	0
Optic nerve disorders NEC		
Optic neuritis	1	0
Paraesthesias and dysaesthesias		
Burning sensation	15	0
Hyperaesthesia	4	0
Paraesthesia	127	0
Paralysis and paresis (excl cranial nerve)		
Diplegia	1	0
Hemiparesis	1	0
Hemiplegia	1	0

Monoplegia	3	0
Paralysis	7	0
Partial simple seizures NEC		
Simple partial seizures	1	0
Peripheral neuropathies NEC		
Neuropathy peripheral	2	0
Seizures and seizure disorders NEC		
Convulsion	15	0
Epilepsy	5	2
Febrile convulsion	8	0
Tonic convulsion	1	0
Sensory abnormalities NEC		
Analgesia	1	0
Dysgeusia	16	0
Hypoaesthesia	53	0
Neuralgia	8	0
Post herpetic neuralgia	1	0
Sensory disturbance	2	0
Sensory loss	4	0
Sleep disturbances NEC		
Poor quality sleep	1	0
Speech and language abnormalities		
Aphonia	3	0
Dysarthria	3	0
Dysphasia	2	0
Speech disorder	3	0
Spinal cord and nerve root disorders NEC		
Radiculitis brachial	1	0
Transient cerebrovascular events		
Transient ischaemic attack	1	0
Tremor (excl congenital)		
Tremor	39	0
Trigeminal disorders		
Facial neuralgia	4	0
Trigeminal nerve paresis	1	0
Lumbar spinal cord and nerve root disorders		
Sciatica	1	0
Multiple sclerosis acute and progressive		
Multiple sclerosis	1	0
Nervous system disorders SOC Total	1465	4

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Pregnancy, puerperium and perinatal conditions		
Foetal position and presentation abnormalities		
Face presentation	1	0
Labour onset and length abnormalities		
Premature labour	3	0
Threatened labour	1	0
Abortions spontaneous		
Abortion spontaneous	25	0
Abortion spontaneous incomplete	1	0
Foetal complications NEC		
Foetal hypokinesia	2	0
Hypertension associated disorders of pregnancy		
HELLP syndrome	1	0
Normal pregnancy, labour and delivery		
Live birth	3	0
Stillbirth and foetal death		
Intra-uterine death	5	5
Stillbirth	2	2
Pregnancy, puerperium and perinatal conditions SOC Total	45	7

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Psychiatric disorders		
Abnormal behaviour NEC		
Abnormal behaviour	2	0
Affect alterations NEC		
Affect lability	1	0
Anxiety symptoms		
Agitation	1	0
Anxiety	5	0
Nervousness	7	0
Tension	1	0
Behaviour and socialisation disturbances		
Aggression	2	0
Personality change	2	0
Communications disorders		
Expressive language disorder	1	0
Confusion and disorientation		
Confusional state	10	0
Disorientation	5	0
Deliria		
Delirium	9	0
Delusional symptoms		
Delusion	1	0
Delusions, mixed	1	0
Depressive disorders		
Agitated depression	1	0
Depression	7	0
Dissociative states		
Depersonalisation	1	0
Dissociation	3	0
Disturbances in initiating and maintaining sleep		
Insomnia	41	0
Eating disorders NEC		
Eating disorder	2	0
Food aversion	1	0

Emotional and mood disturbances NEC		
Crying	3	0
Moaning	1	0
Mood altered	2	0
Emotional distress	1	0
Fluctuating mood symptoms		
Mood swings	1	0
Increased physical activity levels		
Restlessness	6	0
Mental disorders NEC		
Mental disorder	1	0
Mood alterations with depressive symptoms		
Depressed mood	7	0
Tearfulness	2	0
Mood alterations with manic symptoms		
Hypomania	1	0
Mood disorders NEC		
Listless	3	0
Parasomnias		
Abnormal dreams	3	0
Nightmare	9	0
Sleep terror	1	0
Perception disturbances		
Hallucination	8	0
Hallucination, auditory	1	0
Hallucination, visual	2	0
Psychiatric symptoms NEC		
Psychotic disorder NEC		
Acute psychosis	1	0
Psychotic disorder	1	0
Sleep disorders NEC		
Sleep disorder	13	0
Speech articulation and rhythm disturbances		
Stereotypies and automatisms		
Head banging	8	0
Tic disorders		
Tic	1	0
Fear symptoms and phobic disorders (incl social phobia)		
Fear	1	0
Panic attacks and disorders		
Panic attack	2	0

Panic disorder	1	0
Panic reaction	1	0
Psychiatric disorders SOC Total	185	0

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Renal and urinary disorders		
Urinary abnormalities		
Haematuria	1	0
Bladder and urethral symptoms		
Pollakiuria	1	0
Urge incontinence	1	0
Bladder disorders NEC		
Urinary bladder haemorrhage	1	0
Myoneurogenic bladder disorders		
Neurogenic bladder	1	0
Renal failure and impairment		
Renal failure acute	5	0
Urinary tract signs and symptoms NEC		
Renal colic	2	0
Renal pain	7	0
Renal and urinary disorders SOC Total	19	0

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Reproductive system and breast disorders		
Menstruation and uterine bleeding NEC		
Metrorrhagia	1	0
Reproductive tract signs and symptoms NEC		
Pelvic pain	1	0
Genital pain	1	0
Testicular and epididymal disorders NEC		
Testicular swelling	1	0
Vulvovaginal disorders NEC		
Vaginal haemorrhage	2	0
Breast signs and symptoms		
Breast pain	5	0
Breast swelling	1	0
Breast tenderness	1	0
Reproductive system and breast disorders SOC Total	13	0

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Respiratory, thoracic and mediastinal disorders		
Breathing abnormalities		
Dyspnoea	60	0
Hyperventilation	1	0
Hypoventilation	2	0
Tachypnoea	2	0
Bronchospasm and obstruction		
Asthma	27	0
Bronchial obstruction	1	0
Bronchospasm	4	0
Chronic obstructive pulmonary disease	2	0
Wheezing	19	0
Obstructive airways disorder	2	0
Asthmatic crisis	1	0
Coughing and associated symptoms		
Cough	73	0
Haemoptysis	2	0
Productive cough	11	0
Laryngeal spasm, oedema and obstruction		
Stridor	1	0
Lower respiratory tract inflammatory and immunologic conditions		
Pneumonitis	1	0
Nasal disorders NEC		
Epistaxis	11	0
Nasal congestion and inflammations		
Nasal congestion	6	0
Nasal inflammation	1	0
Rhinitis allergic	1	0
Parenchymal lung disorders NEC		
Pulmonary fibrosis	1	1
Pharyngeal disorders (excl infections and neoplasms)		
Pharyngeal oedema	1	0
Pharyngeal hypoaesthesia	1	0
Pulmonary thrombotic and embolic conditions		

Pulmonary embolism	1	1
Paranasal sinus disorders (excl infections and neoplasms)		
Sinus congestion	6	0
Upper respiratory tract signs and symptoms		
Choking	1	0
Dry throat	1	0
Dysphonia	2	0
Rhinorrhoea	48	0
Sneezing	17	0
Throat irritation	3	0
Throat tightness	7	0
Increased upper airway secretion	1	0
Oropharyngeal blistering	1	0
Oropharyngeal pain	95	0
Respiratory failures (excl neonatal)		
Respiratory failure	1	1
Respiratory tract disorders NEC		
Respiratory disorder	2	0
Respiratory tract congestion	3	0
Allergic respiratory disease	1	0
Respiratory, thoracic and mediastinal disorders SOC Total	421	3

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Skin and subcutaneous tissue disorders		
Alopecias		
Alopecia	1	0
Angioedemas		
Angioedema	2	0
Apocrine and eccrine gland disorders		
Cold sweat	9	0
Hyperhidrosis	53	0
Hypohidrosis	1	0
Night sweats	7	0
Sweat gland disorder	8	0
Bullous conditions		
Blister	5	0
Erythema multiforme	6	0
Stevens-Johnson syndrome	2	0
Toxic epidermal necrolysis	1	1
Dermal and epidermal conditions NEC		
Pain of skin	3	0
Skin discolouration	4	0
Skin discomfort	3	0
Skin disorder	1	0
Skin reaction	17	0
Skin warm	2	0
Swelling face	25	0
Hypoaesthesia facial	13	0
Dermatitis and eczema		
Dermatitis	4	0
Dermatitis allergic	8	0
Eczema	5	0
Skin irritation	6	0
Erythemas		
Erythema	46	0
Rash erythematous	15	0
Generalised erythema	1	0

Exfoliative conditions		
Exfoliative rash	1	0
Granulomatous and deep cutaneous inflammatory conditions		
Granuloma annulare	1	0
Panniculitides		
Erythema nodosum	2	0
Papulosquamous conditions		
Parapsoriasis	1	0
Rash papular	3	0
Photosensitivity conditions		
Photosensitivity reaction	2	0
Pilar disorders NEC		
Piloerection	1	0
Purpura and related conditions		
Henoch-Schonlein purpura	1	0
Petechiae	1	0
Purpura	7	0
Pustular conditions		
Rash follicular	1	0
Skin and subcutaneous tissue ulcerations		
Skin ulcer	1	0
Skin injuries and mechanical dermatoses		
Skin vasculitides		
Vasculitic rash	1	0
Skin and subcutaneous conditions NEC		
Palmar-plantar erythrodysaesthesia syndrome	1	0
Urticarias		
Urticaria	58	0
Urticaria papular	3	0
Urticaria physical	1	0
Pruritus NEC		
Pruritus	33	0
Rash pruritic	12	0
Pruritus generalised	22	0
Rashes, eruptions and exanthems NEC		
Rash	102	0
Rash generalised	37	0
Rash macular	18	0
Rash maculo-papular	11	0
Rash morbilliform	1	0
Psoriatic conditions		

Guttate psoriasis	1	0
Psoriasis	1	0
Skin and subcutaneous tissue disorders SOC Total	572	1

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Social circumstances		
Dependents		
Sick relative	1	0
Occupational environmental problems		
Sick building syndrome	1	0
Disability issues		
Disability	1	0
Bedridden	3	0
Impaired driving ability	1	0
Social circumstances SOC Total	7	0

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Surgical and medical procedures		
Therapeutic procedures NEC		
Anaphylaxis treatment	1	0
Obstetric therapeutic procedures		
Forceps delivery	1	0
Surgical and medical procedures SOC Total	2	0

Reaction Name	Reactions	Fatal Reactions
SOC		
HLT		
PT		
Vascular disorders		
Arterial inflammations		
Temporal arteritis	1	0
Circulatory collapse and shock		
Circulatory collapse	18	1
Peripheral circulatory failure	1	0
Neurogenic shock	1	0
Haemorrhages NEC		
Haemorrhage	1	0
Vascular hypertensive disorders NEC		
Hypertension	9	0
Non-site specific necrosis and vascular insufficiency NEC		
Arteriosclerosis	1	0
Infarction	1	0
Peripheral embolism and thrombosis		
Thrombophlebitis	1	0
Peripheral vascular disorders NEC		
Flushing	15	0
Hot flush	16	0
Vasculitides NEC		
Vasculitis	3	0
Vascular hypotensive disorders		
Hypotension	12	0
Orthostatic hypotension	1	0
Site specific vascular disorders NEC		
Pallor	14	0
Vascular disorders SOC Total	95	1