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NOT FOR PUBLICATION


COMMISSION ON HUMAN MEDICINES

BIOLOGICALS AND VACCINES EXPERT ADVISORY GROUP

PHARMACOVIGILANCE EXPERT ADVISORY GROUP

**Title of paper:** Cervarix HPV vaccine – end of routine programme safety review

**Type of paper:** For advice

<b>Product:</b> Cervarix	<b>Marketing Authorisation Holder (MAH):</b> GlaxoSmithKline (GSK) Biologicals S.A.																						
<b>Active Constituent:</b> Human Papillomavirus virus-like particles (HPV types 16 and 18)	<b>Pharmaceutical form:</b> Suspension for injection																						
<b>Therapeutic area:</b> Papillomavirus infections Uterine cervical dysplasia Immunisation <b>ATC code:</b> J07BM02	<b>Legal status:</b> POM																						
<b>Previous assessments:</b> CHM 08/08; 02/09; 06/09; 09/09, 09/10	<b>Assessors:</b> 																						
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## COMMISSION ON HUMAN MEDICINES

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## PHARMACOVIGILANCE EXPERT ADVISORY GROUP

**Cervarix HPV vaccine – end of routine programme safety review****1. ISSUE**

Over 99% of cervical cancer is attributable to human papillomavirus (HPV) infection with greater than 70% of cases related to HPV types 16 and 18. To reduce the burden of disease in the UK, the HPV vaccine Cervarix, containing HPV types 16 and 18, was introduced into the national immunisation programme in September 2008 for adolescent girls aged 12 to 13 years (school year 8) and for a short time period to older girls aged 13 to 18 years as part of a catch-up programme.

From September 2012 Cervarix will be replaced with Gardasil in the routine national HPV immunisation programme. From this date all eligible girls are expected to start and complete the vaccination course using Gardasil. With routine use of Cervarix in the national HPV immunisation programme drawing to a close this report summarises the safety experience of Cervarix within the national HPV immunisation programme up to 31<sup>st</sup> July 2012.

The advice of the Commission on Human Medicines (CHM) and its Pharmacovigilance EAG (PEAG) and Biologicals and Vaccines EAG (BVEAG) is sought on the conclusions of the report.

**2. B BACKGROUND****2.1 Cervical Cancer and HPV**

Worldwide more than 273,000 deaths are from cervical cancer each year and these account for 9% of all female cancer deaths. Increased screening activity in recent years has reduced cervical cancer mortality rates in the UK by nearly 70% in 2008 (2.4 per 100,000 females) compared to 30 years earlier (7.1 per 100,000 females in 1979)<sup>1</sup>. However the cost to patients afflicted is still high with 957 deaths from cervical cancer in 2008 in the UK with an estimated crude rate of 3.1 per 100,000 population.

Over 99% of cervical cancers are caused by human papillomavirus (HPV) infection and of the estimated 100 types of HPV there are about 40 genital HPV types that infect the genital area<sup>2</sup>.

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<sup>1</sup> <http://info.cancerresearchuk.org/cancerstats/types/cervix/mortality/uk-cervical-cancer-mortality-statistics#source1> accessed August 2012

<sup>2</sup> McCance DJ. Papillomaviruses. In: Zuckerman AJ, Banatvala JE, Pattison JR, Griffiths P and Schoub B (eds) *Principles and practice of clinical virology*. 2004 5th edition. Wiley & Sons Ltd.

While some HPV infections can resolve of their own accord, genital HPVs can cause cancer, genital warts, anogenital cancers and cancers of the head and neck<sup>3 4</sup>.

HPV is believed to cause cervical cancer by changing infected epithelial cells. HPV DNA can integrate into human DNA in the cervical epithelial cells at the site of infection and it is this process that is likely to lead to cancer progression<sup>5</sup>. However the exact nature of this process and the role of other factors are not fully understood.

Genital HPVs are classified as 'high-risk' or oncogenic types which cause cervical cancer and early cervical changes and 'low-risk' types, which lead to the development of benign genital warts. In Europe the two main high-risk types, HPV 16 and HPV 18, are together responsible for over 70% of all cervical cancers<sup>6</sup>. While the majority of cases of high-risk HPV infection may not lead to cervical cancer, HPV can cause abnormalities of the cervix which in turn can lead to cervical cancer. Often the time between infection by a high-risk HPV and development of cervical cancer is several years<sup>7</sup>.

It is estimated by the Centers for Disease Control and Prevention that at least 50% of all sexually active women and men are infected by genital HPV at some point in their lives<sup>8</sup>. A study of antibodies to four types of HPV infection (6, 11, 16 and 18) showed that HPV infection in females increases rapidly from 14 to 24 years of age<sup>9</sup> with infection more likely to occur in late teens and early twenties. Abstinence from any sexual activity greatly reduces the risk of genital HPV infection and while condoms also reduce the risk they are not 100% effective<sup>10</sup>.

## **2.2 HPV Vaccines**

In the UK there are two HPV vaccines currently authorised, Cervarix manufactured by GSK and Gardasil manufactured by Sanofi Pasteur MSD.

### **2.2.1 Cervarix**

Cervarix was granted a marketing authorisation by the European Commission on 20<sup>th</sup> September 2007 through the centralised procedure with Belgium as Rapporteur (lead Member State). Cervarix is a suspension for injection that contains purified proteins (L1 proteins) for HPV types 16 and 18. It is available in vials or prefilled syringes and indicated for use from the age of 9 years for the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic HPV types. The indication is based on the

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<sup>3</sup> Parkin DM & Bray F. Chapter 2: The burden of HPV-related cancers. *Vaccine* 2006; **24 S3** S11-25.

<sup>4</sup> Stanley M. Prophylactic HPV vaccines: prospects for eliminating ano-genital cancer. *Br J Cancer* 2007; **96**(9): 1320-3.

<sup>5</sup> Woodman CB *et al*. The natural history of cervical HPV infection: unresolved issues. *Nat Rev Cancer* 2007; **7**(1): 11-22.

<sup>6</sup> Smith JS *et al*. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer* 2007; **121**(3): 621-32.

<sup>7</sup> Moscicki AB *et al*. Chapter 5: Updating the natural history of HPV and anogenital cancer. *Vaccine* 2006; **24 S3** S42-51.

<sup>8</sup> Genital HPV Infection – Fact Sheet. Centers for Disease Control and Prevention (CDC) website <http://www.cdc.gov/std/HPV/STDFact-HPV.htm> accessed August 2012

<sup>9</sup> Jit M *et al*. Prevalence of human papillomavirus antibodies in young female subjects in England. *Br J Cancer* 2007; **97**(7): 989-91.

<sup>10</sup> Koutsky L. Epidemiology of genital human papillomavirus infection. *Am J Med* 1997; **102**(5A): 3-8.

demonstration of vaccine efficacy in women aged 15-25 years and on the immunogenicity of the vaccine in girls and women aged 9-25 years. The clinical development programme to support licensure of the Cervarix consisted of 9 clinical studies<sup>11</sup>.

Cervarix is manufactured by recombinant DNA technology using highly purified virus-like particles (VLPs) of the major capsid L1 protein of oncogenic HPV types 16 and 18. VLPs mimic the structure of the native virus but do not contain any viral DNA. Immunisation with Cervarix elicits an immune response to the L1 proteins assembled in VLPs. Production of antibodies is more rapid following exposure to HPV and thus the risk of diseases caused by HPV types 16 and 18 is reduced. Since the VLPs contain no viral DNA they cannot infect cells, reproduce or cause HPV infection.

Cervarix is made using an adjuvant system that consists of aluminium hydroxide and monophosphoryl lipid A (MPL) known as AS04<sup>12</sup>. MPL is a purified lipid extracted from bacteria, which enhances the response of the immune system to the vaccine.

Cervarix has been registered in 123 countries and since launch up to November 2011, over 28 million doses have been distributed worldwide.

The HPV vaccine has been demonstrated to be over 99% effective in preventing pre-cancerous lesions associated with HPV types 16 and 18 in women who have not already been infected by these types<sup>13 14</sup>. However the vaccine does not protect against disease if HPV infection is already established in the individual. While the vaccine does not protect against all HPV types that cause cervical cancer, there is evidence that Cervarix also provides cross-protection against HPV types 31, 33 and 45, the three most common cancer-causing virus types following types 16 and 18<sup>15</sup>.

In the UK the Joint Committee on Vaccination and Immunisation (JCVI) recommended a vaccine schedule for Cervarix in the national HPV immunisation programme of three doses (0, 1-2 and 6 months) by intramuscular injection for girls in school year 8 (aged 12 to 13 years) over a period of 12 months. When the vaccine was first introduced in September 2008 this was followed by a catch-up programme for older girls between 13 and 18 years of age. Cervarix is considered to be suitable for the majority of adolescent girls and young women although there are a very few individuals who cannot receive the vaccine including those who have had a confirmed anaphylactic reaction to a previous dose of HPV vaccine or to any components of the vaccine. Vaccination is also delayed in those who are pregnant, breast-feeding or those who have a high temperature. Individuals with immunosuppression should be considered for vaccination although these individuals may not develop a full antibody

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<sup>11</sup> Further details of the clinical trials can be found on the European Medicines Agency (EMA) website ([www.ema.europa.eu](http://www.ema.europa.eu)), and the pivotal trials have also been published in the medical literature (e.g. Paavonen *et al.* *The Lancet*. Vol **369**. June 30. 2007).

<sup>12</sup> Adjuvant System 04, a trade name for combination of adjuvants used in various vaccine products by GSK

<sup>13</sup> Ault KA and FUTURE II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. *Lancet* 2007; **369**(9576):1861-8.

<sup>14</sup> Harper DM *et al.* Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet* 2006; **367**(9518): 1247-55.

<sup>15</sup> Paavonen J *et al.* Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types: final event-driven analysis in young women (the PATRICIA trial). *The Lancet*. 2009 Jul 25;**374**(9686):301-14.

response. Prescribing guidance is outlined in the Cervarix Summary of Product Characteristics (annex 1).

In the Cervarix clinical trials involving over 19,000 females the most common adverse reactions observed after vaccine administration were injection site reactions including pain, redness, swelling; fatigue; myalgia and headache with a frequency of very common ( $\geq 1/10$ ) (annex 1). Injection site pain occurred the most frequently (after 78% of all doses). The majority of these reactions were of mild to moderate severity and not long lasting.

Common ( $\geq 1/100$  to  $< 1/10$ ) reactions observed include gastrointestinal symptoms such as nausea, vomiting, diarrhoea and abdominal pain; itching/pruritus; rash; urticaria; arthralgia; and fever ( $\geq 38^{\circ}\text{C}$ ), while reactions identified within the clinical trials as uncommon ( $\geq 1/1000$  to  $< 1/100$ ) include upper respiratory tract infection; dizziness; and other injection site reactions such as induration and local paraesthesia. During the post marketing period lymphadenopathy; allergic reactions (including anaphylactic and anaphylactoid reactions); angioedema; and syncope or vasovagal responses to injection sometimes accompanied by tonic-clonic movements were associated with Cervarix administration and are also listed in the SPC (annex 1).

### **2.2.2 Gardasil**

The second HPV vaccine marketed in the UK is Gardasil and this vaccine was authorised before Cervarix on 20<sup>th</sup> September 2006 by the European Commission. In addition to HPV types 16 and 18 Gardasil contains two extra HPV types (types 6 and 11). HPV types 6 and 11 are responsible for approximately 90% of genital wart cases and Gardasil has been demonstrated to be 99% effective at preventing genital warts caused by specific HPV types<sup>16</sup>. Gardasil is indicated for the prevention of premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer caused by specific HPV types and for the prevention of genital warts (condyloma acuminata).

To date Gardasil has been used to a limited extent in the UK as previously the vaccine had not been procured by the Department of Health for use within the routine national HPV immunisation programme. However from September 2012 Cervarix will be replaced by Gardasil in the national HPV immunisation programme for girls in school year 8 (aged 12 to 13 years). Gardasil has been extensively used in other European countries and in the US with more than 26 million people vaccinated worldwide.

## **2.3 Previous assessments of safety data**

In September 2008 the CHM considered the MHRA's enhanced Pharmacovigilance strategy for Cervarix prior to the start of the national HPV immunisation programme. This included signal evaluation and risk assessment involving daily assessment and categorisation of all suspected new adverse reactions (ADRs); a proactive communication plan (encouraging use of the Yellow Card Scheme and weekly publication of 'Suspected Adverse Reaction Analysis' reports on the MHRA website<sup>17</sup>); safety updates in the Drug Safety Update (DSU) bulletin;

<sup>16</sup> Barr E and Tamms G. Quadrivalent human papillomavirus vaccine. *Clin Infect Dis* 2007; **45**(5): 609-7.

<sup>17</sup> [www.mhra.gov.uk/HPVvaccine](http://www.mhra.gov.uk/HPVvaccine)

weekly teleconferences with the MAH (GSK) to discuss ADRs reported to the Yellow Card Scheme and any new or emerging safety issues identified from non-UK data sources; modified disproportionality analysis methods (Empirical Bayes Geometric Mean or EBGM) to conduct routine and modified signal detection analyses; and proactive and real-time 'observed vs expected' analysis using a statistical sequential test method (Maximised Sequential Probability Ratio Test (MaxSPRT)) of key adverse events of interest to identify possible new risks associated with HPV vaccines (annex 2).

In February 2009 and again in September 2009 (1-year safety review) the CHM reviewed suspected ADRs reported in association with Cervarix but did not identify any new or serious risks. The CHM concluded that the balance of benefits and risks of Cervarix remained positive.

Furthermore in June 2009 the Commission specifically considered reports of chronic fatigue syndrome (CFS) in association with Cervarix. The CHM agreed that the number of cases of suspected CFS and other possible chronic fatigue like syndrome did not represent a safety signal since many more cases would have been expected to occur by chance amongst the number of girls immunised so far. The Commission advised that the available evidence did not support a causal association between Cervarix and CFS but recommended that the issue should be kept under close review. Further analyses of CFS is presented in the Observed/Expected analyses (section 5) and in a study using the UK Clinical Practice Research Datalink (CPRD)<sup>18</sup> (section 6).

In September 2010 a 2-year safety review was presented to the CHM that summarised the UK safety experience of the HPV vaccine following 2 years of use. The review concluded that after 4.5 million doses of Cervarix in the UK the vast majority of suspected ADRs were 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 cases of other medical conditions reported, the available evidence and observed/expected analyses did not suggest that the vaccine caused chronic fatigue syndrome, facial palsy, Guillain Barré Syndrome and encephalitis and these may have been coincidental events. No new risks were identified in association with Cervarix despite significant exposure in the UK. The CHM endorsed the conclusions of the safety review and agreed that the balance of risks and benefits of Cervarix was positive.

### **3. USAGE DATA**

Over 6 million doses of Cervarix have been administered in the UK since the programme started in 2008. While there is some variability in uptake across England, Scotland, Wales and Northern Ireland, the HPV immunisation programme has been considered a success with uptake figures among the highest in the world<sup>19</sup>. During the first three years of the HPV programme, over 65% of all females born between 1 September 1990 and 31 August 1998 completed the three-dose course, with the highest coverage achieved in the youngest cohorts. The proportion of UK females aged 12-13 years receiving doses one, two and three

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<sup>18</sup> Formerly the General Practice Research Database (GPRD)

<sup>19</sup> <http://immunisation.dh.gov.uk/annual-hpv-vaccine-coverage-in-england-in-201011-report>

ranged from 85%, 83.1% and 77.5% in 2009/2010 and 88.4%, 86.6% and 80.9%<sup>20</sup>. More recent provisional data for this past year (1<sup>st</sup> September 2011 to 30<sup>th</sup> June 2012) show uptakes of 90.4%, 89.0% and 82.6% for doses one to three respectively from a cohort of 293,721 year 8 girls aged 12-13 years of age<sup>21</sup>.

Since 2010 the vast majority of vaccine has been administered to girls 12-13 years of age. For example in Wales 41,095 doses of a total of 44,453 doses administered were to those who turned 13 years of age in 2011-2012<sup>22</sup>. This is reflected in the ADR data with the majority of cases reported in females aged 12-13 years (Table 3; section 4.1).

#### **4. SPONTANEOUS ADVERSE REACTION (ADR) DATA**

All suspected adverse reactions (ADRs) associated with Cervarix and HPV brand unspecified received by the Medicines and Healthcare products Regulatory Agency (MHRA) through its spontaneous reporting scheme, the Yellow Card Scheme, up to 31<sup>st</sup> July 2012 were included within the review. This included UK reports received from healthcare professionals, patients and marketing authorisation holders (MAHs). Given that the vast majority of HPV vaccine currently used in the UK is Cervarix provided by the Department of Health within the national HPV immunisation programme, ADR reports that were HPV brand unspecified were also included within the analysis.

##### **4.1 Total ADR Reports**

Since Cervarix was first authorised in the UK the MHRA has received a total of 6213 reports including 14,300 reactions. The total number of reports considered to be serious<sup>23</sup> was 1906 which equates to 31% of the total number of ADR reports. The proportion of serious reports is not unexpected given that a large majority of these reports were psychogenic in nature and due to the injection process and not due to the vaccine *per se* but classified as serious according to the MedDRA (Medical Dictionary for Regulatory Activities) dictionary (e.g. syncope). Section 4.4 of the SPC warns about psychogenic responses to vaccination (annex 1).

The total numbers of reports received by the MHRA by year and by calendar month are presented in Table 1 and Figure 1 respectively.

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<sup>20</sup> Annual HPV vaccine coverage in England: 2009/10 Routine programme for year 8 females (12-13 years old) and catch-up campaign for year 10-13 females (14 -18 years old) DH HPA 22 December 2010

<sup>21</sup> <http://immunisation.dh.gov.uk/hpv-vac-uptake-jun12/>

<sup>22</sup> Data provided by Public Health Wales VPDP (data source National Community Child Health Database of Wales (data extracted July 2012)

<sup>23</sup> Seriousness defined by Council for International Organizations of Medical Sciences (CIOMS) serious flags (fatal, life-threatening, cause hospitalisation, result in persistent or significant disability or incapacity, require intervention to prevent permanent damage, or cause congenital anomalies) or the reporter considered the reaction to be serious. On Sentinel specific 'alert terms' are also considered to be serious

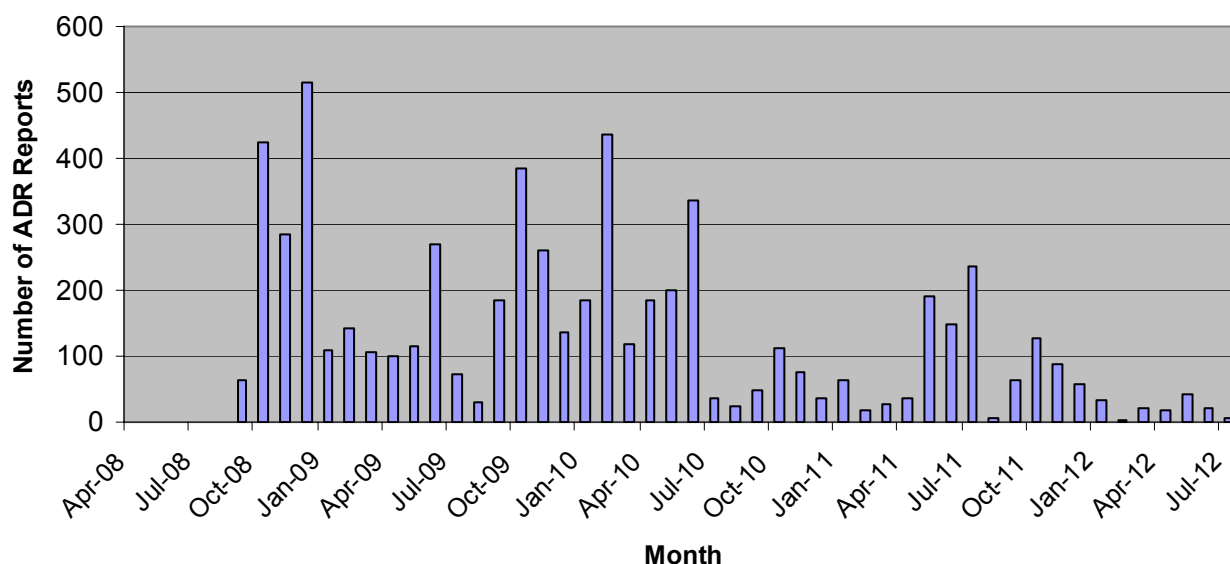
**Table 1. Total number of ADR reports associated with Cervarix and HPV vaccine brand unspecified received by the MHRA by year**

Year received	Number of Reports
2008	1292
2009	1912
2010	1794
2011	1069
2012*	146
<b>Total</b>	<b>6213</b>

\*Data are up to 31<sup>st</sup> July 2012

With over 6 million doses administered the overall reporting rate is estimated to be about 1 report per 1,000 doses administered. This reporting rate is not unexpected for a newly marketed vaccine used within a new national immunisation programme with such high vaccine exposure over a four year period.

**Figure 1. Number of ADR reports associated with Cervarix and HPV vaccine brand unspecified (April 2008 to July 2012)**



At the time of initial use of Cervarix within the national HPV immunisation programme healthcare professionals involved in the immunisation programme were contacted to encourage reporting of ADRs via the Yellow Card Scheme. As a new Black Triangle ▼

vaccine<sup>24</sup> for use in adolescents the initial high level of ADR reporting was not unexpected. Exposure was greatest during the initial two years of the immunisation programme when the catch-up programme was used to vaccinate females 14 to 18 years in addition to those 12-13 years of age. In recent years ADR reporting levels have fallen with only 146 reports thus far in 2012 despite vaccination uptake remaining consistently over 80% in the routine cohort,. Overall the reporting levels are not considered unusually high for a new vaccine used at a national level.

The number of ADR reports by reporter source (Table 2) highlights the large contribution made by nurses to the Yellow Card Scheme throughout this vaccination programme with nurses contributing to two thirds of all reports received by the Agency. As the main administrators of the vaccine in schools they were well placed to observe and then report ADRs to the Agency and their valuable contribution is recognised.

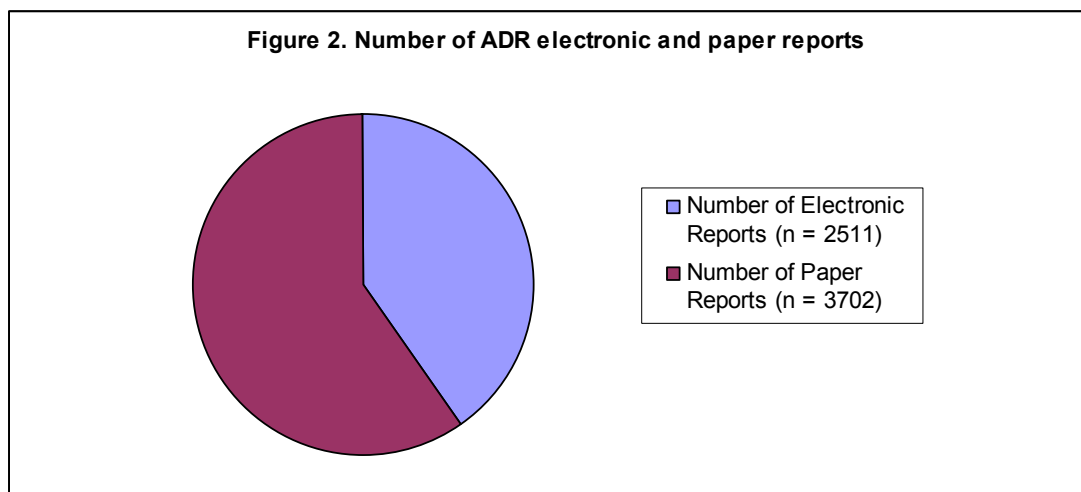
**Table 2. The number and percentage of ADR reports by reporter source**

<b>Reporter Qualification</b>	<b>Number of Reports</b>	<b>Percentage of Reports</b>
UNKNOWN	3	0.05 %
HOSPITAL PHARMACIST	5	0.08 %
CARER	10	0.16 %
COMMUNITY PHARMACIST	10	0.16 %
PHARMACIST	38	0.59 %
PATIENT	41	0.64 %
HOSPITAL DOCTOR	91	1.42 %
PHYSICIAN	97	1.52 %
HOSPITAL HEALTHCARE PROFESSIONAL	100	1.56 %
CONSUMER OR OTHER NON HEALTH PROFESSIONAL	155	2.42 %
PARENT	194	3.03 %
HOSPITAL NURSE	299	4.67 %
GP	399	6.23 %
OTHER HEALTHCARE PROFESSIONAL	681	10.6 %
NURSE	4280	66.8 %
<b>Total:</b>	<b>6403*</b>	<b>100 %</b>

\*The total number of reports is higher than 6213 as some reports contain more than one reporter (e.g. a parent and a healthcare professional)

Figure 2 shows a change in trend from the 2-year review in which a greater proportion of electronic reports were received while recent data up to 31<sup>st</sup> July 2012 show a greater proportion of paper reports than electronic reports for Cervarix and HPV brand unspecified.

<sup>24</sup><http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/BlackTriangleproducts/index.htm>



Reports received broken down by patient age are presented in Table 3. As expected the majority of cases were reported in individuals of the appropriate age specified within the national HPV vaccination programme which is currently year 8 (aged 12-13 year olds) and when the catch up programme was initially implemented in those <18 years of age. There have been 20 reports in patients <10 years of age and the vast majority of these were reported in those less than 2 years of age (parent-child reports). The safety of Cervarix during pregnancy is discussed in section 4.8 below. A single case was reported in a 7 year-old but this is likely to be a reporting error on behalf of the reporter.

**Table 3. The number and percentage of ADR reports by age of the patient**

Ages	Number of Reports	Percentage of Reports
<10 years	20	0.32 %
10 Years	2	0.03 %
11 Years	13	0.21 %
12 Years	2283	36.75 %
13 Years	1128	18.16 %
14 Years	458	7.37 %
15 Years	645	10.38 %
16 Years	454	7.31 %
17 Years	622	10.01 %
18 Years	277	4.46 %
19 Years	23	0.37 %
20 Years	3	0.05 %
21 Years	2	0.03%
22 Years	1	0.02 %
23 Years	1	0.02 %

24 Years	1	0.02 %
25 Years	1	0.02 %
26 Years	2	0.03 %
27 Years	1	0.02 %
30 Years	1	0.02 %
31 Years	1	0.02 %
32 Years	1	0.02 %
37 Years	1	0.02 %
53 Years	1	0.02 %
Unknown	271	4.36 %
<b>Total</b>	<b>6213</b>	<b>100 %</b>

The number of reports broken down by MedDRA (Medical Dictionary for Regulatory Activities) terminology System Organ Class is provided in Table 4. A further breakdown of the number of reactions by high-level term (HLT) and preferred term (PT) in each SOC are at annex 3. Events of interest in specific SOCs and those terms that are likely to be of interest to those administering or using the vaccine are described below.

**Table 4. Total number and percentage of adverse reactions by MedDRA System Organ Class**

<b>MedDRA System Organ Class (SOC)</b>	<b>No. of Adverse Reactions</b>	<b>Percentage of Adverse Reactions</b>
Nervous system disorders	4263	29.81 %
General disorders and administration site conditions	2940	20.56 %
Gastrointestinal disorders	2100	14.69 %
Musculoskeletal and connective tissue disorders	1455	10.17 %
Skin and subcutaneous tissue disorders	1301	9.10 %
Vascular disorders	436	3.05 %
Respiratory, thoracic and mediastinal disorders	370	2.59 %
Eye disorders	281	1.97 %
Psychiatric disorders	232	1.62 %
Investigations	185	1.29 %
Immune system disorders	123	0.86 %
Infections and infestations	118	0.83 %
Injury, poisoning and procedural complications	95	0.66 %
Reproductive system and breast disorders	72	0.50 %
Cardiac disorders	68	0.48 %
Metabolism and nutrition disorders	59	0.41 %
Ear and labyrinth disorders	57	0.40 %
Blood and lymphatic system disorders	36	0.25 %
Congenital, familial and genetic disorders	33	0.23 %
Pregnancy, puerperium and perinatal conditions	31	0.22 %
Renal and urinary disorders	16	0.11 %
Surgical and medical procedures	11	0.08 %
Neoplasms benign, malignant and unspecified (including cysts and polyps)	9	0.06 %
Endocrine disorders	5	0.03 %
Social circumstances	3	0.02 %
Hepatobiliary disorders	1	0.01 %
<b>Total</b>	<b>14300</b>	<b>100 %</b>

## 4.2 Reports with a fatal outcome

There have been two cases with a fatal outcome associated with Cervarix since authorisation. Both these cases were presented in the 2-year review from September 2010. There was no indication that Cervarix caused or contributed to the unfortunate fatal events. No additional cases with fatal outcomes have been reported since the period of the review. Case details are provided below.

[REDACTED]

[REDACTED]

## 4.3 Nervous System Disorders

The SOC with the greatest number of reports (4263) was the Nervous System Disorders SOC (29.81%). Within this SOC the highest numbers of suspected adverse reactions include headache (1128), dizziness (1367), syncope (501), hypoaesthesia (251), paraesthesia (148) and tremor (110). These reactions or related terms are included within the product information (annex 1).

Within the 2-year review a total of 892 reports containing 2236 reactions (19% of total reports) were classified as psychogenic events based on signs / symptoms of a fear or anticipatory response to the needle injection. This includes terms such as dizziness and nausea in the context of syncope, loss of consciousness/ altered state of consciousness, vision disturbance (including transient blindness), injury, limb jerking (often misinterpreted/ reported as a seizure/convulsion), limb numbness or tingling and difficulty in breathing. A warning to highlight these psychogenic reactions has been added to section 4.4 of the Cervarix SPC (annex 1) given that this population is particularly prone to these type of reactions.

Other events of interest within this SOC include Guillain-Barré Syndrome, encephalitis and Bell's palsy (VIIth nerve paralysis/facial palsy) and convulsions.

#### 4.3.1 Guillain-Barré Syndrome

At the time of the 2-year review the MHRA had received 5 reports of Guillain-Barré Syndrome (GBS). These reports are detailed as follows:

█ [REDACTED]

█ [REDACTED]

█ [REDACTED]

█ [REDACTED]

- A female of unspecified age was reported as developing suspected GBS and at unspecified time after vaccination. Despite follow-up, no further information was available.

All 5 cases of GBS were included in the Observed/Expected analysis using MaxSPRT test method (annex 2). Two cases were included in the first year's analysis (2008-2009) and three in the second year's analysis (2009-2010). Given the expected background incidence of GBS

in the vaccinated population, the 'observed' vs 'expected' analyses suggested that the reported cases are consistent with chance and there was no evidence of a safety signal for GBS.

Since the 2-year review there have been no additional cases of GBS associated with Cervarix or HPV unspecified. The absence of additional cases within the past two years despite a further 1.5 million doses administered supports the previous position that GBS is unlikely to be causally related with Cervarix.

#### 4.3.2 Encephalitis

There have been 6 reports of encephalitis and 1 report of encephalitis lethargica reported to date. The first 5 cases were previously reported within the 2-year review and described below.

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

- A female of unknown age was reported by a pharmacist as developing encephalitis at an unspecified time after vaccination with Cervarix. No further details are available despite follow-up.
- A female of unknown age was reported by a practice nurse as developing encephalitis at an unspecified time after vaccination with a 3rd dose of Cervarix. No further details are available despite follow-up.

Since then 2 additional cases have been reported:

■ [REDACTED]

[REDACTED]

[REDACTED]

Within the 2-year review the MaxSPRT analysis suggested the cases reported were consistent with chance (annex 2). Three of the cases previously reviewed refer to NMDA receptor antibody encephalitis. This is a form of acute encephalitis caused by an autoimmune reaction against NR1- and NR2- subunits of the glutamate NMDA receptor that is responsible for controlling memory function and synaptic plasticity. The disease is generally associated with tumours<sup>25</sup> although not all cases are found to have evidence of tumours. Although the background incidence of anti-NMDA encephalitis, and the prevalence of anti-NMDA antibodies in the healthy population, is not known the available medical literature appears to indicate a preponderance of the condition in adolescent females (even without ovarian tumours).

Neither of the two new cases have been directly medically confirmed as the parents of the children reported encephalitis in both cases. In the first case the reaction was initially classified as chronic fatigue syndrome and the parent provided follow-up information [REDACTED]

[REDACTED] Nevertheless the first case has been added for the Observed/Expected Analyses (see section 5). The second case occurred post May 2012 (the time cut-off for which usage data used in the analysis) and therefore was not included within the analysis. However details of this case are sparse and the diagnosis of encephalitis is questionable as the case refers to “encephalitic reaction” and this has not been medically confirmed.

#### **4.3.3 Bell’s palsy (VIIth nerve paralysis / Facial palsy)**

A total of 9 reports of Bell’s palsy (VIIth nerve paralysis / Facial palsy) have been reported to date. This includes 5 unique reports facial palsy reported in the previous 2-year review:

[REDACTED]

<sup>25</sup> Dalmau J *et al.* Paraneoplastic Anti–N-methyl-D-aspartate Receptor Encephalitis Associated with Ovarian Teratoma. *Ann. Neurol.* Jan 2007; **61**(1):25–36.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

An additional case was not reported as facial palsy but the case details were suggestive of possible facial palsy and was therefore included in the 2-year analysis:

[REDACTED]

All 5 confirmed cases of facial palsy and the one additional possible case were included in the previous MaxSPRT analysis (annex 2). Two cases were included in the first year's analysis and four in the second year's analysis. The results for both years did not indicate a signal for any reporting level in either year.

Since 28<sup>th</sup> July 2010 (the cut-off date for the 2-year review) the MHRA has received an additional three reports:

[REDACTED]

[REDACTED]

[REDACTED]

Two of these cases occurred within the defined time period and are included within the Observed/Expected analysis (section 5).

Following a review of the Rapporteur's assessment of the 7<sup>th</sup> Periodic Safety Update Report (PSUR), covering the period 18<sup>th</sup> November 2010 to 17<sup>th</sup> November 2011, in April 2012 the MHRA requested the submission of a cumulative review by the MAH of all cases of Bell's palsy / VIIth nerve paralysis / facial paresis within a 3 month period from the time of the request. All case details including temporal associations and patient past medical histories were requested where available. This review is pending.

#### **4.3.4 Convulsions**

There have been a total of 97 seizures and seizure disorders reported including convulsion (74), grand mal convulsion (11), clonic convulsion (1) and other reactions. At the time of the 2-year review there were 31 reports of convulsion and 7 reports of grand mal convulsion plus other reactions. The majority of cases of convulsion were reported in association with other reactions such as loss of consciousness / syncope or with additional conditions. Tonic clonic movements are listed in the SPC in the context of psychogenic events associated with syncope (annex 1). There is currently insufficient evidence of a causal association of Cervarix with convulsions that are not psychogenic in nature. Convulsions will continue to be monitored.

#### **4.3.5 Complex regional pain syndrome**

Up to 31<sup>st</sup> July 2012 six cases of complex regional pain syndrome have been reported:

[REDACTED]

[REDACTED]

- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Complex regional pain syndrome (CRPS) is characterised by severe pain, swelling and changes in the skin temperature and colour of the arms or legs. The cause of the syndrome is unknown but common predisposing conditions include trauma, infection, surgery, cervical radiculopathy, soft tissue contusions, fractures, tendon ruptures and myocardial infarction.

Data on the incidence of CRPS are scarce and mostly hospital based. A retrospective cohort study conducted from 1996 to 2005 in the Integrated Primary Care Information (IPCI), a general practice research database with electronic patient record data from 600,000 patients across the Netherlands, estimates the overall incidence rate of CRPS as 26.2 per 100,000

person years (95% CI: 23.0-29.7)<sup>26</sup>. In this study the highest incidence occurred in females in the age category 61-70 years. The upper extremity was affected more frequently than the lower extremity and a fracture was the most common precipitating event (44%). Another study of the 1990 population (n=106,470) medical records from the Mayo Clinic and Olmsted Medical Group in Minnesota estimates the incidence rate as being much lower at 5.46 per 100,000 person years at risk with the most common trigger fracture reported at a similar rate (46%)<sup>27</sup> as the other study.

The syndrome has been associated with vaccines such as rubella and Hepatitis B vaccines. While there is a clear temporal association in the majority of cases associated with the HPV vaccine CRPS may be more likely attributed to needle trauma, as proposed by Genc *et al.*, 2005<sup>28</sup>, rather than the vaccine constituents. It is also possible that such reports were coincidental.

In order to further evaluate this signal the 'snapshot' Observed / Expected method was used for analysis using the incidence rates 26.2 per 100,000 person years and 5.46 per 100,000 person years taken from the two published studies. Using these incidence rates and usage data from September 2008 up to the end of May 2012 the Observed / Expected ratios were calculated as 0.03 (95% CI 0.01-0.07) and 0.16 (95% CI 0.06-0.35) respectively. While this is a crude analysis using incidence rates not restricted to 12-18 year old females, in both cases since the O/E ratios are well below 1 these data indicate that the observed number of events are well below the events expected for this event in 12-18 year old girls who have received Cervarix. Cases of CRPS will continue to be monitored.

#### **4.4 General disorders and administration site conditions**

This was the SOC with the second highest number of reactions reported (2940 ADRs; 20.56%) with the vast majority relating to injection site reactions (652 in HLT), fatigue (378), malaise (499), pyrexia (319) / feeling hot (147), peripheral oedema (229) and pain (128). The majority of these reactions are listed in the SPC (annex 1).

Events of interest include Chronic Fatigue Syndrome (CFS) / Myalgic encephalomyelitis (ME)

##### **4.4.1 Chronic Fatigue Syndrome (CFS) / Myalgic encephalomyelitis (ME)**

Chronic Fatigue Syndrome (CFS) is diagnosed when other possible diagnoses have been excluded. In June 2009, CHM considered a specific safety paper which assessed reports of CFS and chronic fatigue in temporal association with Cervarix vaccine. At the time MHRA had received 1 report of CFS, 4 reports of post viral fatigue syndrome<sup>29</sup>, and two reports of 'chronic' fatigue. An additional 3 cases of Chronic Fatigue-like Syndrome separately reported in the media were also assessed. The CHM advised that the available evidence did not support a causal association between Cervarix and CFS.

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<sup>26</sup> De Mos M *et al.* The incidence of complex regional pain syndrome: a population-based study. *Pain* 2007; **129**(1-2):12-20.

<sup>27</sup> Sandroni P *et al.* Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. *Pain* 2003; **103**(1-2):199-207.

<sup>28</sup> Genc H *et al.* Complex regional pain syndrome type-I after rubella vaccine. *Eur J Pain* 2005; **9**(5): 517-520.

<sup>29</sup> Myalgic encephalomyelitis codes to post viral fatigue syndrome in MedDRA

At the time of the 2-year review (up to 28<sup>th</sup> July 2010) the MHRA had received 4 reports of CFS and 6 reports of post-viral fatigue syndrome (see annex 2). Results of the MaxSPRT analysis for both 2008-2009 and 2009-2010 suggested that the reported cases were consistent with chance and this was supported by the lack of consistent temporal association and clinical characteristics of the reported cases of CFS/ME. Since that time period the MHRA has received an additional 10 cases of CFS within the past two years presented below.

1 [REDACTED]

2 [REDACTED]

3 [REDACTED]

4 [REDACTED]

5 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

A total of eight cases of CFS/ME and post viral fatigue syndrome (section 4.5.1) have been included within the Observed / Expected Analyses as these reaction onset dates occurred within the defined time period (section 5).

## **4.5 Infections and Infestations**

### **4.5.1 Post Viral Fatigue Syndrome**

Post viral fatigue syndrome (PVFS) codes to the Infections and Infestations SOC. Up to 31<sup>st</sup> July 2012 there have been 16 reports of PVFS. Up to 28<sup>th</sup> July 2010 the MHRA had received 7 reports of post-viral fatigue syndrome (see annex 2).

As 3 of the PVFS cases describe CFS/ME (see section 4.4.1), only the remaining 6 cases are detailed below.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

A total of eight cases of CFS/ME (section 4.4.1) and post viral fatigue syndrome have been included within the Observed / Expected Analyses (section 5).

#### **4.6 Immune System Disorders**

Within the Immune System Disorders SOC there have been a total of 123 reactions of which 63 are reported as an anaphylactic /anaphylactoid reaction. Compared with the 2-year review 47 cases of anaphylaxis /anaphylactoid reactions were reported at that time point with the majority of cases containing insufficient details to suggest true anaphylaxis as defined by the Brighton criteria. Even in the unlikely event that all reported cases were true anaphylaxis, a reporting rate of 63 cases per 6,000,000 doses administered would be consistent with broad estimates of vaccine-induced anaphylaxis. Allergic reactions including anaphylactic and anaphylactoid reactions are listed in the SPC and patients known to be hypersensitive to the active substance or the excipients are contraindicated from vaccine administration (annex 1).

#### **4.7 Neoplasms**

There have been a total of 9 neoplastic reactions within the Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps) SOC including medulloblastoma, acute lymphocytic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia, neoplasm malignant, benign hydatidiform mole, salivary gland cancer stage 1, anogenital warts and skin papilloma. This includes a case with a fatal outcome of 1a malignant tumour of the chest (see section 4.2). These cases do not suggest that Cervarix is associated with an increased neoplastic risk.

#### **4.8 Pregnancy and Congenital Anomalies**

Cervarix is not recommended during pregnancy. During the Cervarix clinical development program, a total of 3,993 pregnancies were reported including 2,009 in women who had received Cervarix (annex 1). Overall, the proportions of pregnant subjects who experienced specific outcomes (e.g., normal infant, abnormal infants including congenital anomalies, premature birth, and spontaneous abortion) were similar between treatment groups. Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development.

Within the Pregnancy, Puerperium and Perinatal conditions SOC there have been a total of 31 ADRs reported (Table 5) and a further 33 ADRs within the Congenital, Familial and Genetic disorders SOC (Table 6).

**Table 5. Pregnancy, Puerperium and Perinatal conditions SOC**

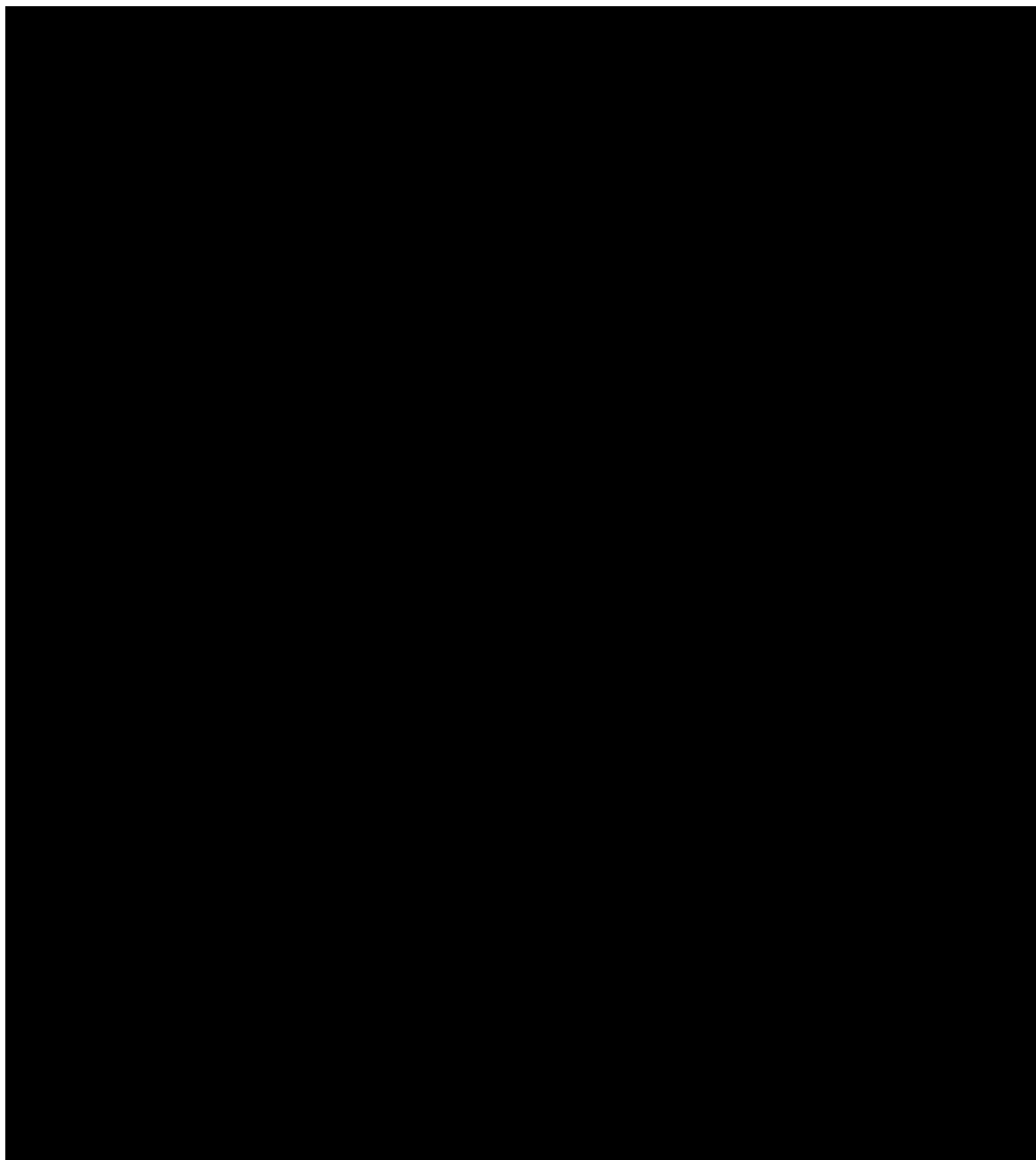
Reaction Preferred Terms	Number
Abortion spontaneous	14
Foetal distress syndrome	1
Foetal growth restriction	2
Premature baby	5
Premature labour	1
Labour complication	1
Live birth	5
Foetal death	1
Pregnancy with injectable contraceptive	1
<b>Total</b>	<b>31</b>

**Table 6. Congenital, Familial and Genetic Disorders SOC**

Reaction Preferred Terms	Number
PRETERNATURAL ANUS	2
ATRIOVENTRICULAR SEPTAL DEFECT	2
CEREBRAL PALSY	1
CONGENITAL ANOMALY	1
VACTERL SYNDROME	2
DOUBLE OUTLET RIGHT VENTRICLE	2
HYPOSPADIAS	1
LIMB HYPOPLASIA CONGENITAL	2
LIMB REDUCTION DEFECT	2
TALIPES	1
SPINE MALFORMATION	2
CLEFT PALATE	1
HIGH ARCHED PALATE	1
PULMONARY APLASIA	2
PULMONARY HYPOPLASIA	2
CONGENITAL CYSTIC KIDNEY DISEASE	2
BIRTH MARK	1
ICHTHYOSIS	1
PILONIDAL CYST CONGENITAL	2
SEBACEOUS NAEVUS	1
ANKYLOGLOSSIA CONGENITAL	1
ARTERIOVENOUS MALFORMATION	1
<b>Total</b>	<b>33</b>

There is no clear pattern to suggest that Cervarix use during pregnancy results in a specific congenital abnormality or is associated with a high risk of spontaneous abortion. This is supported by pregnancy outcome data<sup>30</sup> collated by both the Health Protection Agency (HPA) using their Vaccines in Pregnancy (VIP) registry and the UK Teratology Information Service (UKTIS).

In the recent renewal procedure the MAH presented their worldwide pregnancy outcome data during post-marketing (Table 7).



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<sup>30</sup> Unpublished data

<sup>31</sup> MAH data extracted from Rapporteurs' Joint Preliminary Assessment Report – Cervarix EMEA/H/C/721/R/35 dated 23<sup>rd</sup> May 2012

GSK will be conducting a post-marketing safety study to assess the risk of spontaneous abortions during the first 23 weeks of gestation in women aged 15 to 25 years exposed to Cervarix in the UK using the CPRD.

The inadvertent use of Cervarix during pregnancy will continue to be closely monitored.

## **5. OBSERVED / EXPECTED ANALYSES**

As part of the enhanced pharmacovigilance strategy and presented within the 2-year review, age-specific and gender-specific background incidence rates for a range of 'events of interest' were calculated on a weekly basis using 10 years of historical data from GPRD. Incidence rates were used to estimate the expected number of reports on a continuous cumulative basis. A cumulative relative risk was calculated each week based on the cumulative sum of certain ADR reports received as the 'observed' and the cumulative incidence rate and the cumulative exposure deriving the 'expected'. A sensitivity analysis adjusted the expected number of reports for varying degrees of under-reporting.

The statistical sequential test method, the Maximised Sequential Probability Ratio Test (MaxSPRT), was used to compare the number of reported cases of suspected side effects of interest against the normal rates of such illnesses that are expected to occur by chance in the vaccinated age groups to determine if the vaccine may carry any excess risks. These analyses adjust for various levels of possible under-reporting through the Yellow Card Scheme. The method signals when the observed number of reports exceeds the expected based on a critical value derived from the poisson distribution. Sequential methods are useful to adjust for the multiple testing that occurs with weekly surveillance. 'Observed vs expected' analyses were conducted weekly over two 1 year periods 2008/2009 and 2009/2010 (see annex 2).

### **5.1 Observed vs. Expected analyses for 2010/11 and 2011/12**

Analyses were conducted for Guillain-Barré syndrome, Bell's / facial palsy, chronic fatigue syndrome / post viral fatigue syndrome and encephalitis for the academic years 2010/11 and 2011/12. The latest available exposure data (number of girls vaccinated) was available up to 31<sup>st</sup> May 2012 for England, March 2012 for Wales and between June-Aug 2011 for Scotland and Northern Ireland.

Cases received between September 2010 and 31<sup>st</sup> July 2012 were included within the analyses if the reaction onset date was between these dates.

There were a few retrospective cases of chronic fatigue syndrome and Bell's palsy for which the reaction dates were in the timeframes that have been documented before i.e. 2008-09 and 2009-10. However these cases were not included in the analysis.

#### **5.1.1 Chronic fatigue syndrome/ME and Post viral fatigue syndrome**

From September 2010 to August 2011 there were 5 cases of CFS reported in girls aged 12-13 years. There were 3 cases reported during September 2011 and May 2012. No signals were observed for any of the reporting levels (Figures 3 and 4).

Figure 3

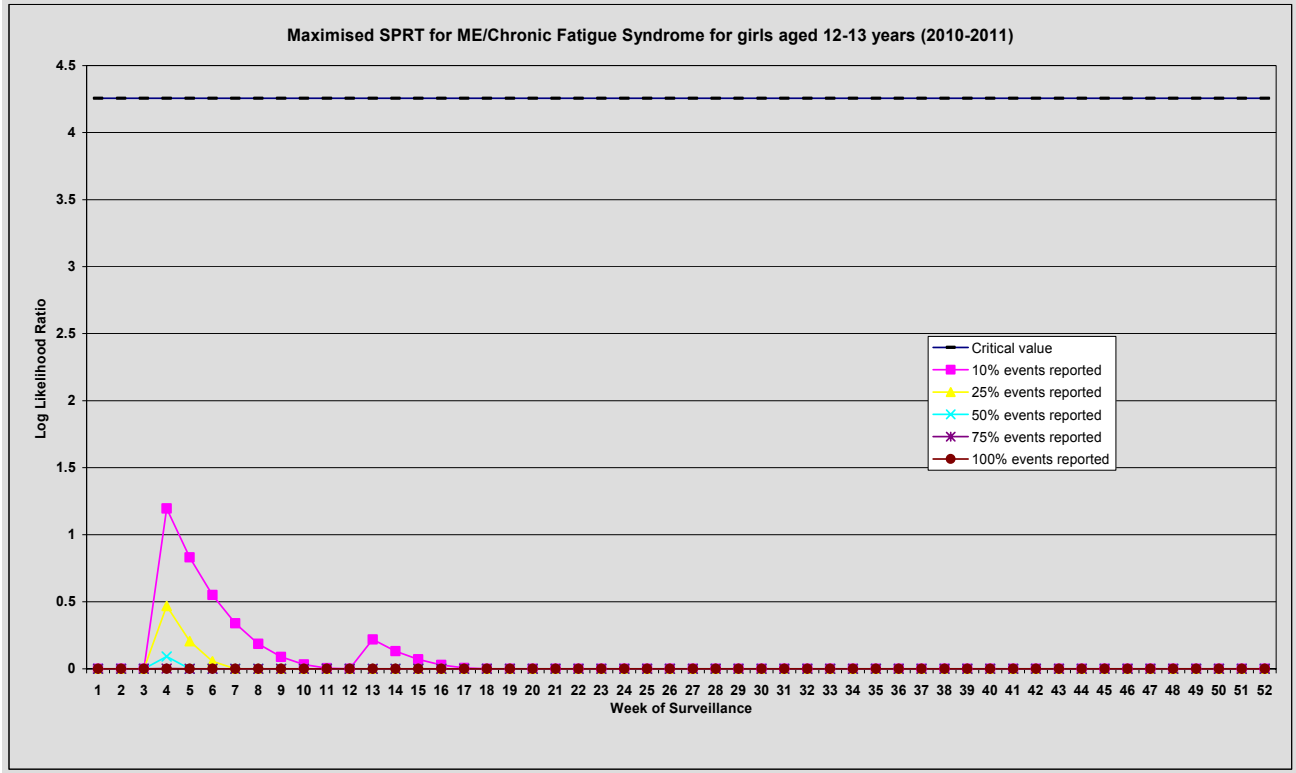
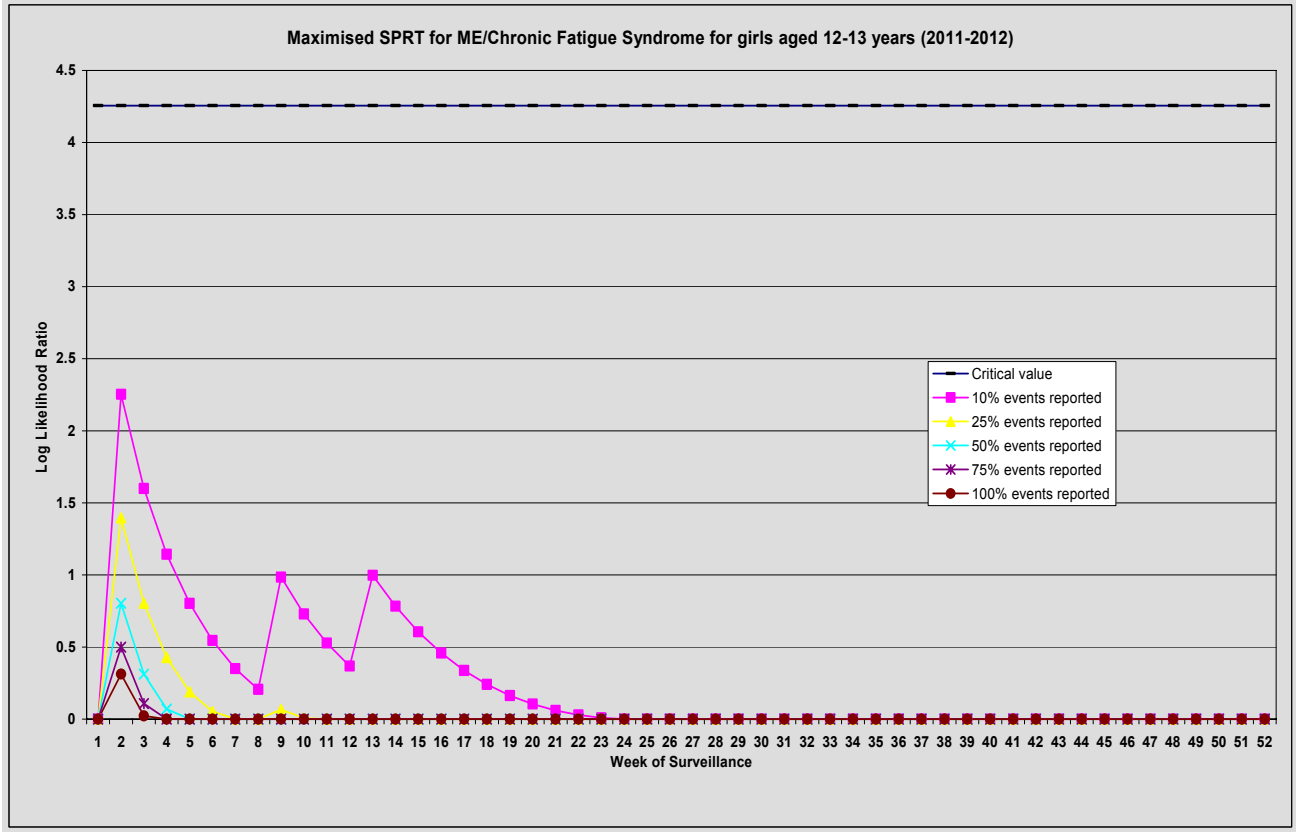


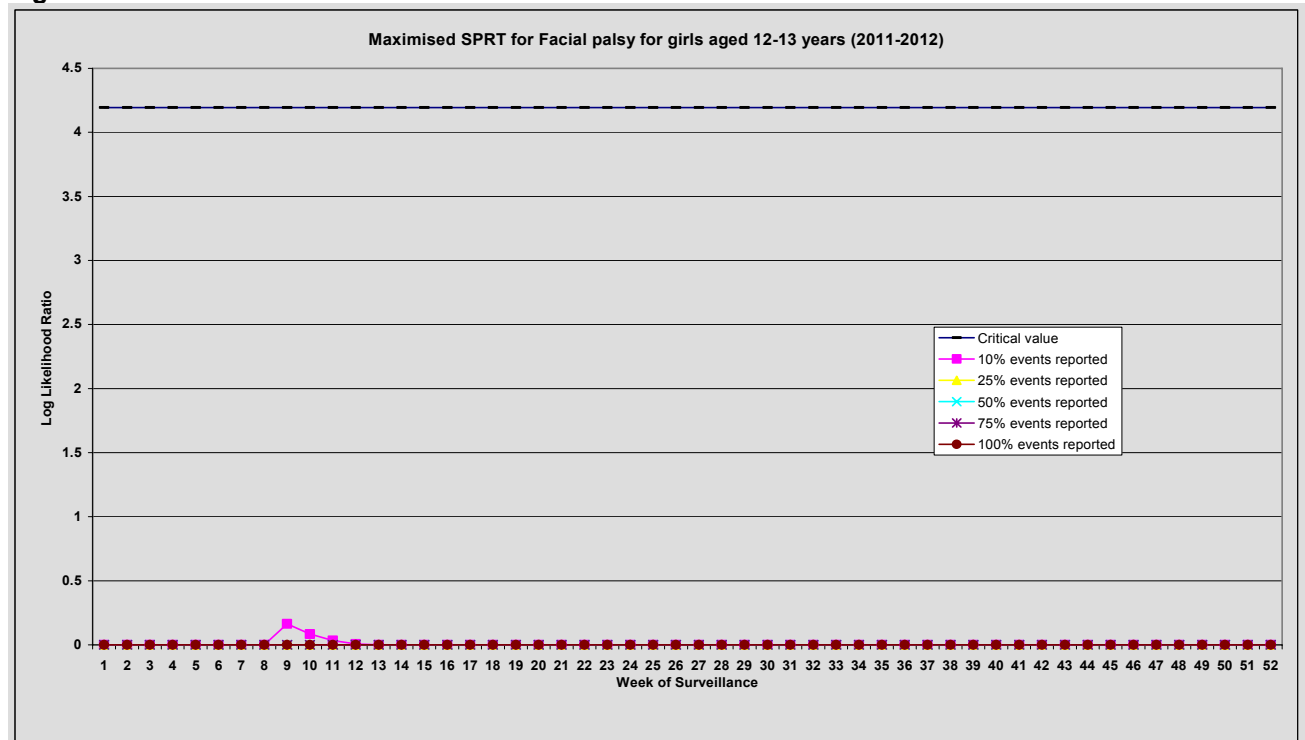
Figure 4



### 5.1.2 Bell's palsy/VIIIth nerve paralysis

There were two cases of Bell's palsy / VIIIth nerve paralysis reported during Sept 2011 and May 2012 and the analysis does not indicate a signal for any reporting level (Figure 5).

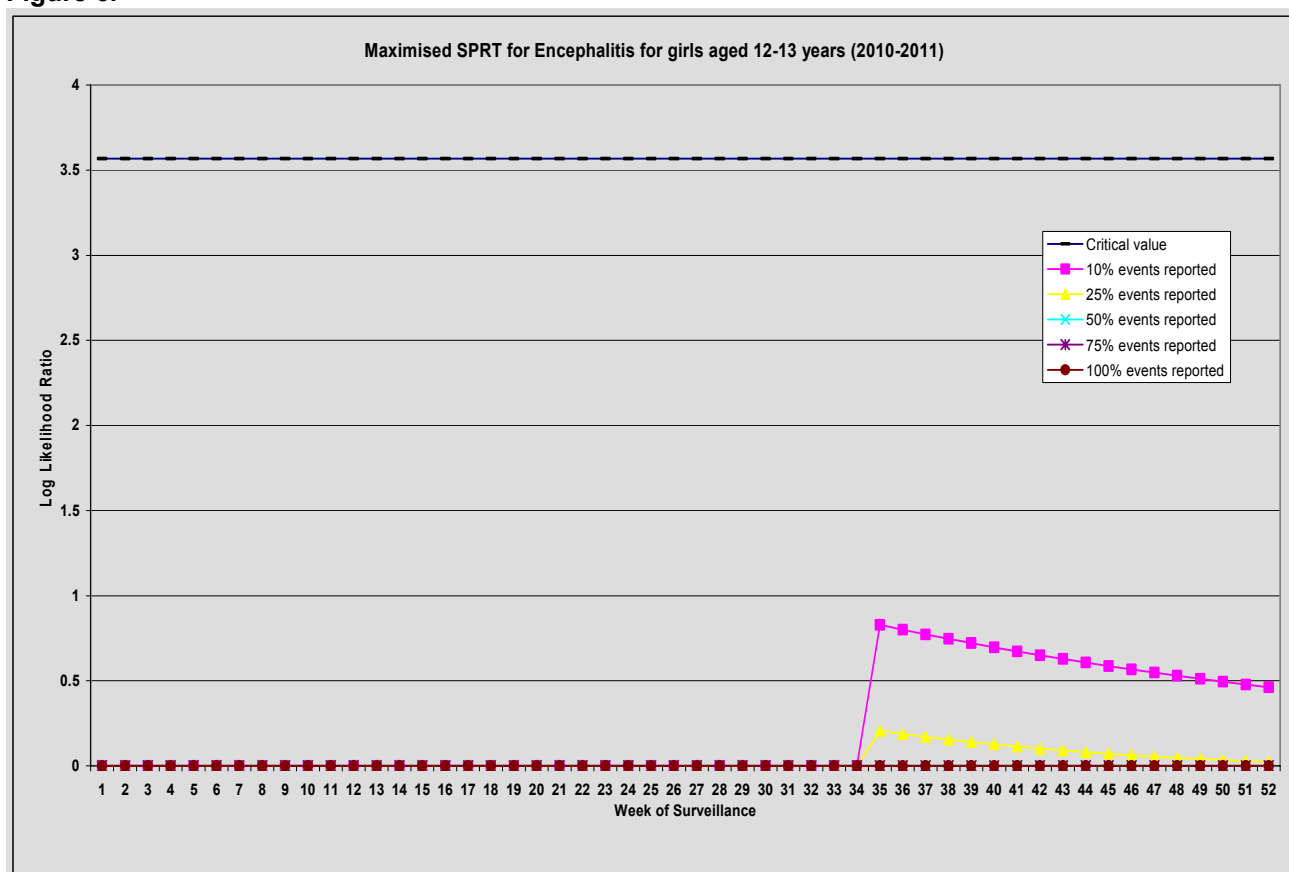
**Figure 5**



### 5.1.3 Encephalitis

There was one case of encephalitis reported during September 2010 and August 2011 and the analysis does not indicate a signal for any reporting level (figure 6). No events were reported between September 2011 and May 2012.

**Figure 6.**



### Conclusion on observed vs expected analyses

Previous incidence rates calculated for the 2-year review were used to estimate the expected number of reports. Unlike the 2-year review which calculated cumulative relative risks each week for a 2 year period these data were calculated retrospectively to provide 'snapshot' Observed / Expected analyses. While the conclusions that can be drawn from these data are limited as a number of assumptions have been made, the data do not suggest that any of the events of interest are greater than the critical threshold. Therefore the number of observed cases is not greater than expected and no new safety signals have been identified for the events of interest Guillain-Barré syndrome, Bell's / facial palsy, chronic fatigue syndrome / post viral fatigue syndrome and encephalitis using this methodology during the periods 2010/2011 and 2011/2012.

## **6. UK Clinical Practice Research Datalink (CPRD) Study: Human Papillomavirus vaccine and the risk of fatigue syndrome in children in the UK**

### **6.1 Purpose**

This section of the paper considers the results of a study which uses the UK Clinical Practice Research Datalink (CPRD, formerly the General Practice Research Database or GPRD) to investigate the potential association between human papillomavirus (HPV) vaccination and the occurrence of fatigue syndrome in girls in the UK. The aim is to provide information on any potential association prior to the switch in the UK from the use of Cervarix in the national vaccination program to the alternative product Gardasil.

### **6.2 Background**

The UK HPV immunisation programme commenced in September 2008, with routine immunisation of 12-13 yr old females and an initial catch-up of females aged up to 18 years. The vaccine programme has been very successful. During the first three years of the programme, over 65% of all females born between 1 September 1990 and 31 August 1998 completed the three-dose course. The highest coverage has been achieved in the youngest cohorts, with more than 84% of 12- to 13-year-old females completing the three-dose course. More than 5 million doses were administered up to December 2011.

### **6.3 CPRD study**

#### **6.3.1 Objectives**

The aim of this study is to investigate the potential association between HPV vaccination and the occurrence of fatigue syndrome in females in the UK using two different approaches:

1. To describe trends in the recording of fatigue diagnoses in 12 to 20 years old girls in the CPRD before and after the introduction of the vaccination campaign (Ecological study).
2. To carry out a self-controlled case series (SCCS) study to investigate the temporal relationship between HPV vaccination and fatigue diagnoses in females in the CPRD.

#### **6.3.2 Methods**

##### **Ecological study**

Patients with a clinical diagnosis of fatigue syndrome (annex 4 - Appendix A) were extracted from the Clinical Practice Research Datalink (CPRD) general practice database, in March 2012. Data up to 31 December 2011 were included. An incident diagnosis was defined as the first recorded clinical diagnosis per acceptable patient during active follow up in an up-to-standard practice.

The incidence of fatigue syndromes, in girls aged 12-20 years, was calculated overall, by category of first diagnosis (chronic fatigue syndrome, post viral fatigue syndrome,

fibromyalgia, and neuralgia). Where missing, month of birth was randomly assigned. The incidence rate of diagnosis is presented by year 2000-2011.

Poisson regression was used to compare trends in incidence rates before (2006-2007) and after (2009-2011) the introduction of the HPV vaccination campaign.

Sensitivity analyses examining the incidence in adults aged 21+ years and boys aged 12-20 years were conducted using the same inclusion criteria as before. In addition, a further sensitivity analysis, conducted only in girls aged 12-20 years, including referrals for fatigue syndromes and symptoms (annex 4 - Appendix B), as well as records of clinical diagnoses, was conducted. Again only records occurring in acceptable patients during active follow up in an up-to-standard practice were included.

### **Self-controlled case series study**

Self-controlled case series (SCCS) methodology was developed to investigate associations between acute outcomes and transient exposures, using only data on cases. In a case series analysis only cases are sampled with the likelihood of an event occurring in a pre-defined risk period compared to other non-risk periods within the same individual. All fixed covariates are therefore implicitly controlled for while age or other temporal variation can be adjusted for in the model. In brief, an overall study time-window, usually defined by age and calendar time boundaries (but also in terms of vaccination date), is chosen. Then, all individuals with an event within this study time-window are identified. The vaccination dates of each case are then used to define one or more risk periods, during which individuals are hypothesized to be at increased (or reduced) risk of the event of interest after or before vaccination. All other time within an individual's observation period, that does not fall within a risk period, is included in that individual's control period, which together form the study baseline. Estimation of parameters in the SCCS method is achieved by fitting a conditional Poisson regression model.

Girls with a record of a first vaccination (as a clinical or immunisation record, see Appendix C of annex 4) followed by an incident diagnosis of a fatigue syndrome, occurring when in active follow up in an up-to-standard practice, were included in the main analysis. Note that vaccination is, in general, conducted by school nurses and then reported to the GP. In each SCCS analysis, only girls with a recorded first vaccination (as recorded explicitly using the correct clinical/immunisation code in Appendix C of annex 4) were included with this date used as the index date for the main analysis. Patients with any diagnosis (including symptoms and referrals) prior to their first vaccination were excluded. Patients with less than one year of active follow up, in their most recent registration period, in an up-to-standard practice prior to their first vaccination were also excluded to try and ensure identification of incident cases. The risk window was defined to start the day after the date of first vaccination and continue for one year. The index date for the primary analysis was the date of the first clinical diagnosis of fatigue syndrome. Time before vaccination was not considered unexposed and was excluded from the analysis, as the occurrence of fatigue syndrome may affect the likelihood of vaccination, so the time from one year post first vaccination to the date of last follow up was considered as the not at risk period. Age, in years, was adjusted for as a discrete time varying covariate. All cases identified in the main analysis were investigated in further detail. Summaries of the time from vaccination to first diagnosis are presented as well as the dates of diagnosis.

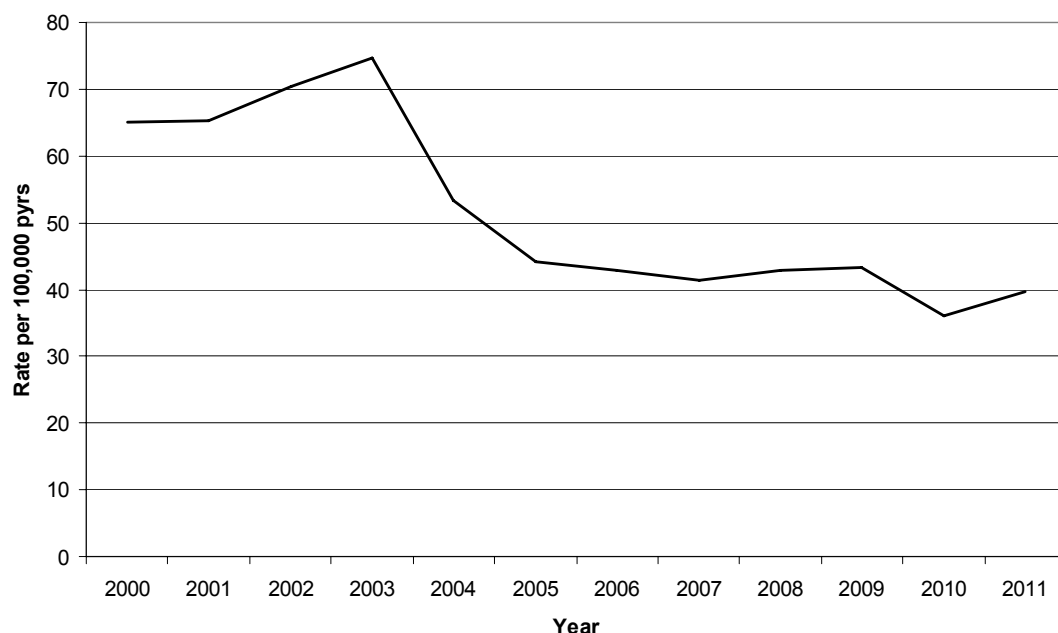
The first sensitivity analyses included cases with a prescription record for a HPV vaccination (annex 4 - Appendix C) and not an immunisation date, assuming the prescription date is the same as the vaccination date. Given that HPV vaccination would not be prescribed in the normal sense the accuracy of this assumption may be doubted hence they are not included in the main analysis. The index date of first clinical diagnosis remained the same. A second sensitivity analysis, including first referrals for, and symptoms of, fatigue syndromes as well as clinical diagnoses was also considered. The index date in this second sensitivity was therefore defined as the first record of symptoms, referral, or diagnosis occurring when in active follow up in an up-to-standard practice. Again, patients with any diagnosis (including symptoms and referrals) prior to their first vaccination were excluded. Finally, a further analysis using a shorter risk window of 6 months was considered defining the not at risk period as all time from 6 months post date of vaccination to the date of last follow up as the not at risk period.

### 6.3.3 Results

#### Ecological study

1,294 first clinical diagnoses of fatigue syndromes were identified in girls aged 12-20 years between 2000 and 2011 in the CPRD. Figure 6.1 shows the rate of first diagnoses of fatigue syndromes in girls aged 12-20 years by year.

**Figure 6.1: Rate of first diagnoses of fatigue syndromes in girls aged 12-20 years 2000-2011.**

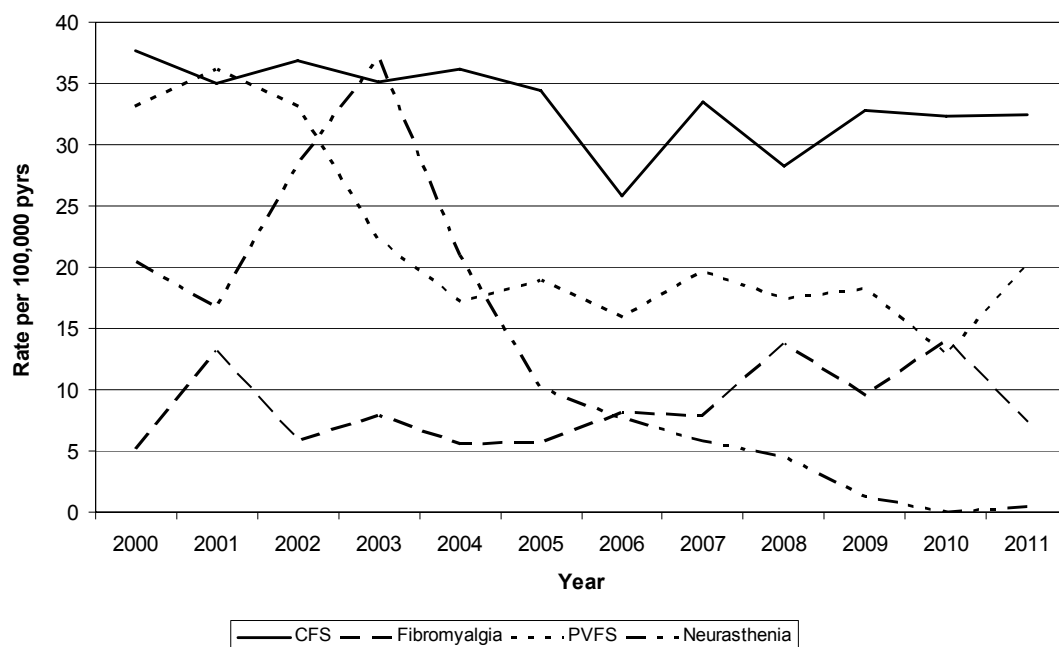


From 2003 to 2005 there was a steep decline in the rate of diagnosis of fatigue syndromes in this group. From 2006 onwards the rate of diagnosis appears to have plateaued with perhaps a small further temporary decline in 2010. Comparing the incidence rate of diagnoses in 2009-2011 to 2006-2007 results in an incident rate ratio of IRR=0.94 (95% confidence

interval: 0.78-1.14, two-sided  $p=0.52$ ) suggesting that there has been no change in the incidence of fatigue syndromes in girls aged 12-20 years since the introduction of the HPV vaccination.

Figure 6.2 shows the rate of incident diagnoses of fatigue syndromes in girls aged 12-20 years by year stratified by the type of diagnosis. It can be seen that the decrease in diagnosis of fatigue syndromes between 2003 and 2005 was driven by a steep decline in the diagnosis of, firstly, post viral fatigue syndrome (PVFS) and, secondly, neurasthenia. There was no obvious trend in the diagnosis of chronic fatigue syndrome or fibromyalgia during the same period. Again, when comparing the rate of diagnosis for each category of fatigue syndrome 2006-2007 with 2009-2011, there has been no change in the rate of diagnosis of chronic fatigue syndrome, fibromyalgia, or PVFS ( $p>0.2$ ). However, there has been a very significant decrease in the diagnosis of neurasthenia (IRR 0.08, 95% CI: 0.02-0.24,  $p<0.001$ ).

**Figure 6.2: Rate of first diagnoses of fatigue syndromes in girls aged 12-20 years 2000-2011 by type of diagnosis.**



It is clear that changes in recording practices have occurred over the study period, therefore, it is important to examine these trends in both boys aged 12-20 years and adults aged 21+ years to check that a decrease in the recording or making of a diagnosis is not masking an increase in the incidence of true diagnoses.

Figure 6.3, showing the analysis from the first sensitivity analysis, shows that the decrease in recording seen in girls aged 12-20 years between 2003 and 2005 was also seen across the rest of the patient population. As with the girls, a non-significant decrease in the incidence of fatigue syndromes has been seen in adults (0.96, 0.93-1.01,  $p=0.11$ ). However, in boys aged 12-20 there has been a significant decrease in the diagnosis of fatigue syndromes (2009/11 vs. 2006/7, IRR: 0.66, 95% CI: 0.50-0.87,  $p=0.002$ ).

**Figure 6.3: Sensitivity analysis I - Rate of first diagnoses of fatigue syndromes 2000-2011 by age and gender.**

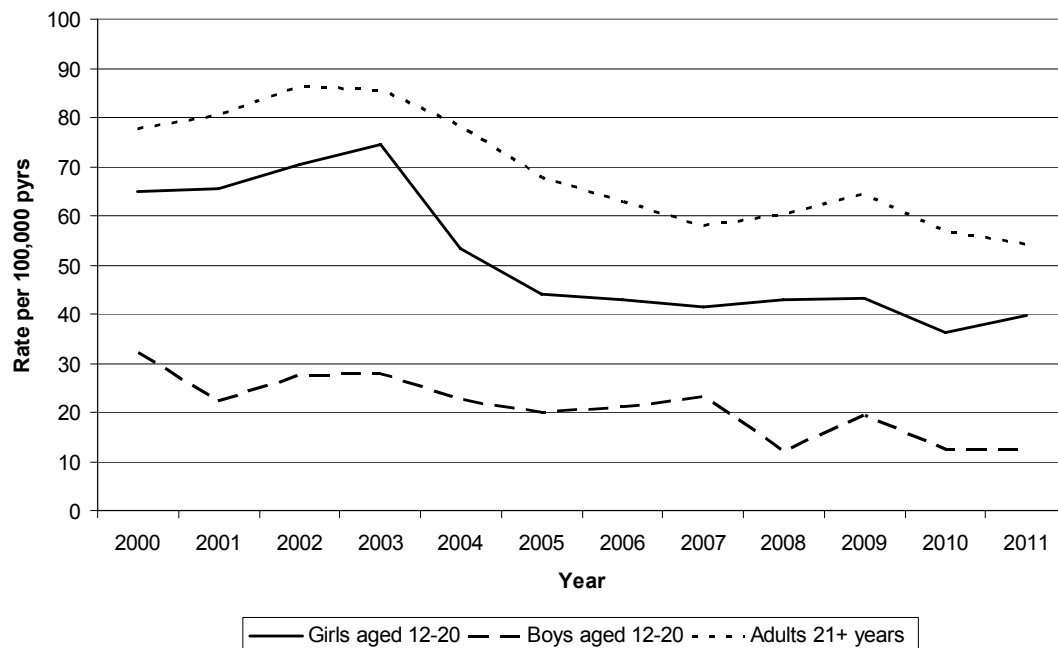
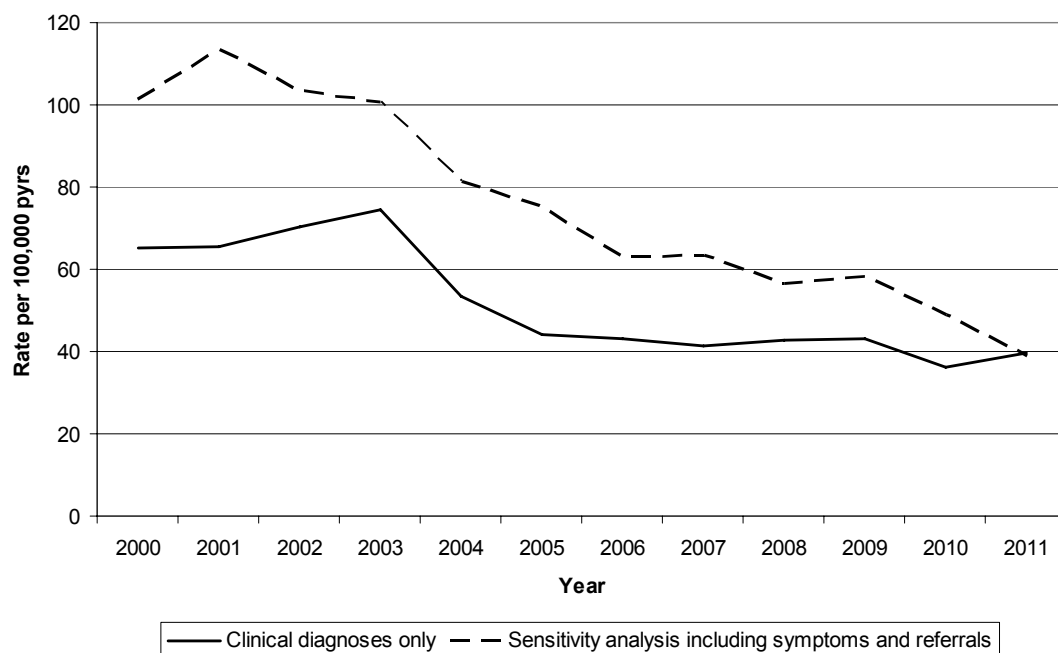


Figure 6.4 shows the results from the second sensitivity analysis, in girls 12-20 years, where referrals for fatigue syndromes and symptoms are also included.

**Figure 6.4: Sensitivity analysis II - Rate of first diagnoses of fatigue syndromes 2000-2011 including symptoms and referrals.**



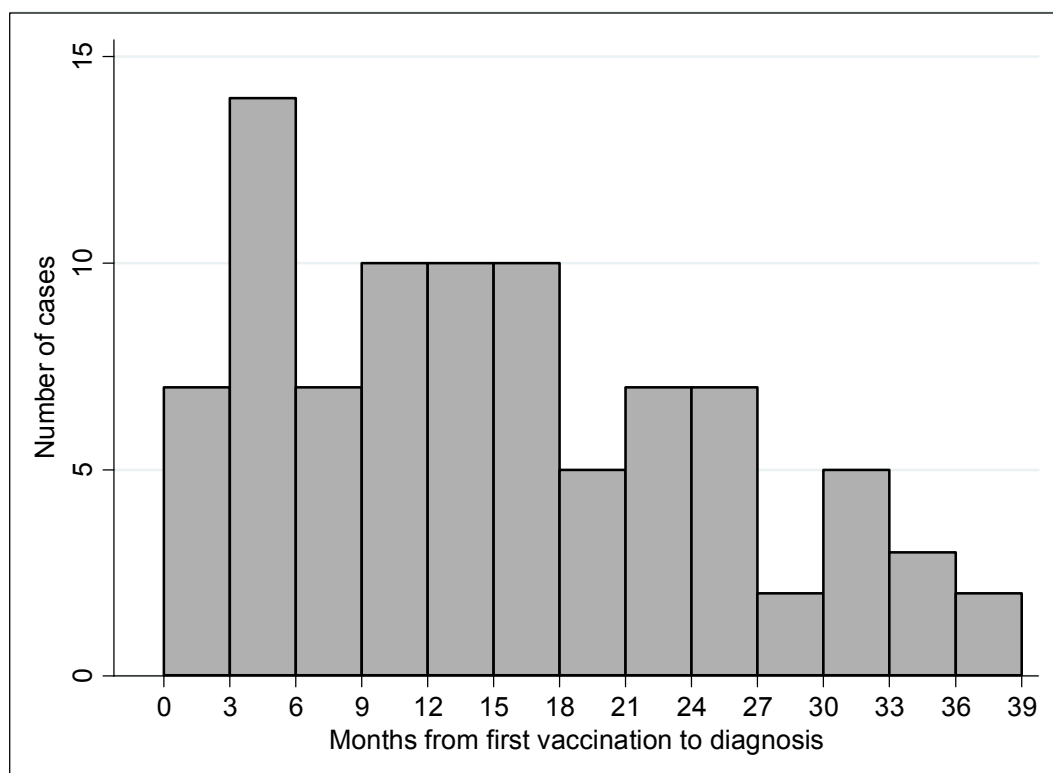
The decrease in clinical diagnoses 2003 to 2005 was also seen when including symptoms and referrals (Figure 6.4). However, beyond that a further reduction has been seen (2009/11 vs. 2006/7 IRR: 0.77, 95% CI: 0.66-0.91,  $p < 0.001$ ) not seen when only considering clinical diagnoses.

### Self-controlled case series study

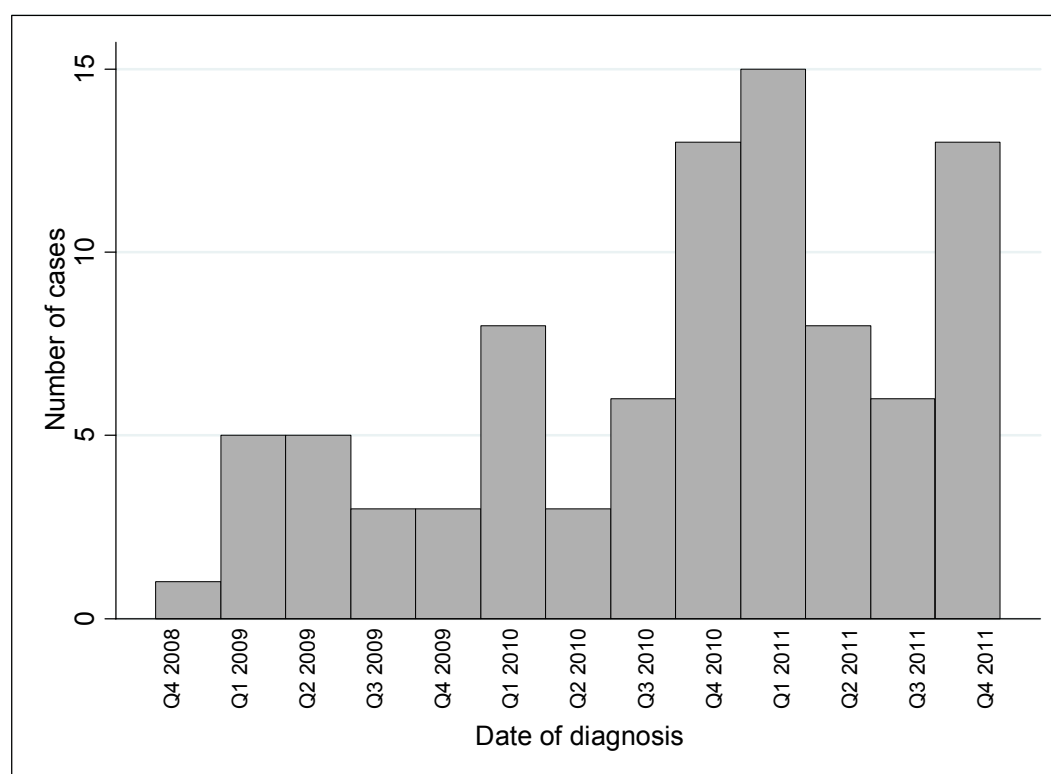
In the main analysis 89 girls with an incident clinical diagnosis of a fatigue syndrome after their recorded first vaccination with the HPV vaccine were identified according to the stated inclusion criteria. 78 (93%) and 57 (78%) were after a further second and third vaccinations respectively although dates of second and third vaccinations were recorded in only 84 and 73 of the girls.

The distributions of time from vaccination to and diagnosis and dates of diagnosis are shown in Figures 6.5 and 6.6 respectively.

**Figure 6.5: Time from first vaccination to diagnosis for 89 cases**



**Figure 6.6: Dates of diagnosis of fatigue syndrome for 89 cases**



The median (IQR) time, from date of first vaccination to diagnosis of fatigue syndrome was 13.9 (6.9-22.2) months. 38 cases were diagnosed in the one year risk window. There was a peak in the number of cases identified in Q4 2010 and Q1 2011 although this could be due to either an increase in fatigue syndrome or an increase in recording of vaccination at that time. Patients were followed for a median 2.3 (IQR: 2.0-3.1) years following the date of first vaccination.

59 (66%) cases had no recorded symptoms or a referral to a specialist prior to the first diagnosis of fatigue syndrome. Only 29 had symptoms of tiredness recorded prior to their first diagnosis with a median (IQR) time of 5.9 (1.9-8.6) months between first symptoms and diagnosis. Nine had a specialist referral a median (IQR) 8.3 (3.4-22.9) weeks prior to diagnosis. Also, of note, a further 10 girls had a first referral a median (IQR) 3.4 (0.1-25.1) weeks after their first recorded diagnosis date.

The conditional Poisson regression model estimated a non-significant decreased risk of fatigue syndrome following HPV vaccination (IRR: 0.87, 95% CI: 0.43-1.72, p=0.68). As expected, an increasing risk with age was also seen (full results not presented).

Several sensitivity analyses were conducted. The first, including prescription records for HPV vaccination (95 cases in total), also showed a non-significant decreased risk (IRR: 0.82, 95% CI: 0.42-1.59, p=0.55).

Similarly, the second, where the index date was defined as the first symptoms of, referral for, or diagnosis of a fatigue syndrome also estimated a non-significant decreased risk of fatigue syndrome within one year of first HPV vaccination (IRR: 0.77, 95% CI: 0.39-1.51, p=0.45). 92

patients were included in this analysis (3 had no clinical diagnosis recorded so were not included in the main analysis) with a median 14.0 (IQR: 7.1-23.0) months between vaccination and event date.

Finally, a non-significant increased risk is observed in the main analysis if the risk period is shortened to 6 months (IQR: 1.13, 95% CI: 0.56-2.25  $p=0.74$ ). In this model, 21 events occurred in the risk window.

#### **6.3.4 Discussion**

The first section of this study, the ecological analysis, showed no difference in the incidence of fatigue syndrome in girls aged 12-20 years in 2009-2011 compared to the years immediately before the introduction of the HPV vaccination (2006-2007). However, a trend was observed of decreasing diagnosis in the earlier years 2003-2005. A similar pattern was seen in adults aged 21+ years. However, in boys aged 12-20 this trend was seen to continue with a further decrease in diagnosis in 2009-2011 compared to 2006-2007. This ecological analysis does not suggest the possibility of a large increased risk but it does indicate a need for further controlled analyses.

Before commencing with the self controlled case series the quality of the data in the CPRD to examine the association of HPV vaccine with an increased risk of fatigue syndromes was considered. The GP data in the CPRD has been extensively used for epidemiological studies of all kinds and several self controlled case studies. However, to date, there are no publications using the database to examine HPV vaccination. The completeness of the HPV vaccination data is of some concern as only 30-40% of girls have any record of a HPV vaccination (either first, second, or third dose) despite accurate data collected by the NHS showing generally more than 80% of girls receive the full three doses (and an even greater percentage receiving at least one dose). In general, we might assume that the data is missing completely at random, meaning that results from the SCCS are unbiased, although it may be dependent on other factors such as medical history, geographical differences in how the vaccine programme is delivered, or media attention which could lead to selection biases. Additionally, there may also be a concern around the accuracy of the recorded vaccination dates given the delay in reporting by the school nurse to the GP.

Several complications arise in the studying of fatigue syndromes. The insidious onset of the conditions can lead to recall bias regarding the onset of symptoms. Moreover, the diagnosis of fatigue syndromes is usually one of elimination meaning that the diagnoses seen here, prior to referral to a specialist, may be premature and unconfirmed. However, the self controlled case series provided no evidence of an increased risk of fatigue syndrome.

As with all observational studies of this type, an increased risk of fatigue syndrome with HPV vaccination cannot be ruled out, particularly due to the high level of missing exposure data and the difficult nature of the diagnosis. However, it can be concluded that this study found no evidence of an association between HPV vaccine and fatigue syndromes based on the available data within the CPRD.

## 7. DISCUSSION

In September 2008 Cervarix was first routinely used in the UK for the prevention of premalignant cervical lesions and cervical cancer in female adolescents in a national HPV immunisation programme. The vaccine is expected to prevent up to 400 deaths due to cervical cancer each year in the UK. Since Cervarix was introduced its safety has been closely monitored through an enhanced pharmacovigilance strategy and recently in a more routine manner. When a vaccine is administered to so many people over a relatively short time period, it is inevitable that some vaccine recipients will develop medical conditions not long after vaccination. For such conditions that also occur naturally in the absence of vaccination, their occurrence shortly after vaccination does not necessarily mean that the vaccine caused the condition. Previous reviews of the safety of Cervarix concluded that the balance of benefits and risks of the HPV vaccine were positive.

With the imminent switch from Cervarix to Gardasil within the HPV immunisation programme this report summarises the safety experience of Cervarix in the UK including consideration of usage data, suspected ADRs received through the Yellow Card Scheme with a closer review of events of interest using Observed/Expected analyses. These data are supplemented with a CPRD study that specifically investigated the potential association between HPV vaccination and fatigue syndromes in girls in the UK.

It is estimated that over 6 million doses of Cervarix have been administered in the UK since authorisation in 2007. While there is some variability in uptake across the UK, the HPV immunisation programme has been considered a success with uptake figures generally >80% across all doses administered and these are among the highest uptake figures in the world<sup>32</sup>. During the first couple of years of the programme there was greater usage of the vaccine with a catch-up campaign for older girls between 13 and 18 years of age in addition to school year 8 (aged 12 to 13 years). In recent years the vast majority of vaccine is administered to girls 12-13 years of age.

Since Cervarix was first authorised in the UK up to 31<sup>st</sup> July 2012 the MHRA has received a total of 6213 reports including 14,300 reactions. With over 6 million doses administered the overall reporting rate is estimated to be about 1 report per 1,000 doses administered. Overall the reporting rate is not unexpected for a newly marketed vaccine used within a novel national immunisation programme. In recent years ADR reporting levels have fallen despite continued high use. Two thirds of the reports originated from nurses and as the main administrators of the vaccine their valuable contribution to the Yellow Card Scheme is recognised.

Approximately 31% of all reports received were coded as serious. The proportion of serious reports is not unexpected given that a large majority of these reports were psychogenic in nature and due to the injection process and not due to the vaccine *per se* but classified as serious according to the MedDRA dictionary. Section 4.4 of the SPC warns about psychogenic responses to vaccination as this population is particularly prone to these events (annex 1). Reporting of serious ADRs may also have been influenced by the MHRA's communication to healthcare professionals at the start of the HPV vaccine programme to encourage the use of the Yellow Card Scheme.

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<sup>32</sup> <http://immunisation.dh.gov.uk/annual-hpv-vaccine-coverage-in-england-in-201011-report>

Since authorisation there have been two reports with fatal outcomes associated with Cervarix and both of these were presented previously in the 2-year review from September 2010. There was no indication that the vaccine caused or contributed to the *Streptococcal* sepsis or malignant neoplasm reported in these cases.

Nervous system disorders was the SOC with the greatest number of ADRs (n=4263, 29.81%) with the majority of reactions listed in the SPC or considered psychogenic events based on signs / symptoms of a fear or anticipatory response to the needle injection.

As part of the enhanced pharmacovigilance strategy and presented 'events of interest' including Guillain-Barré Syndrome (GBS), encephalitis, Bell's palsy (VIIth nerve paralysis/facial palsy) and chronic fatigue syndrome / post viral fatigue syndrome were analysed using Observed / Expected analyses and MasSPRT within the 2-year review (annex 2). New 'snapshot' Observed / Expected analyses were conducted for these events of interest for the academic years 2010/11 and 2011/12 (section 5).

### **Guillain-Barré Syndrome**

At the time of the 2-year review the MHRA had received 5 reports of GBS. Since then there have not been any additional cases of GBS associated with Cervarix or HPV brand unspecified. The absence of additional cases within the past two years despite a further 1.5 million doses administered supports the previous position that GBS is unlikely to be causally related with Cervarix.

### **Bell's palsy (VIIth nerve paralysis / Facial palsy)**

A total of 9 reports of Bell's palsy (VIIth nerve paralysis / Facial palsy) have been reported to date. This includes 5 unique reports facial palsy reported in the previous 2-year review. There were two cases of Bell's palsy / VIIth nerve paralysis reported during Sept 2011 and May 2012 and the MaxSPRT analysis does not indicate a signal for any reporting level (Figure 5). In April 2012 the MHRA requested the submission of a cumulative review by the MAH of all cases of Bell's palsy / VIIth nerve paralysis / facial paresis within a 3 month period from the time of the request. All case details including temporal associations and patient past medical histories were requested where available. This review is pending.

### **Encephalitis**

There have been 6 reports of encephalitis and 1 report of encephalitis lethargica reported to date. The first 5 cases were previously reported within the 2-year review and the MaxSPRT analysis suggested the cases reported were consistent with chance (annex 2). There was one case of encephalitis reported during September 2010 and August 2011 and the analysis does not indicate a signal for any reporting level (Figure 6). Three of the cases previously reviewed refer to NMDA receptor antibody encephalitis a form of acute encephalitis caused by an autoimmune reaction against NR1- and NR2- subunits of the glutamate NMDA receptor. Although the background incidence of anti-NMDA encephalitis, and the prevalence of anti-NMDA antibodies in the healthy population, is not known the available medical literature appears to indicate a preponderance of the condition in adolescent females (even without ovarian tumours).

### **Chronic Fatigue Syndrome / Myalgic encephalomyelitis / Post viral fatigue syndrome**

Chronic Fatigue Syndrome (CFS) / Myalgic encephalomyelitis (ME) has been extensively reviewed. In June 2009, CHM considered the risk of CFS and chronic fatigue with Cervarix.

The CHM advised that the available evidence did not support a causal association between Cervarix and CFS. At the time of the 2-year review (up to 28<sup>th</sup> July 2010) the MHRA had received 4 reports of CFS and 6 reports of post-viral fatigue syndrome. Results of the MaxSPRT analysis for both 2008-2009 and 2009-2010 suggested that the reported cases were consistent with chance and this was supported by the lack of consistent temporal association and clinical characteristics of the reported cases of CFS/ME (annex 2). Using the same conservative approach as within the 2-year review, cases of both CFS/ME and post viral fatigue syndrome were included within the Observed / Expected Analyses (section 5). Since the time of the 2-year review the MHRA has received an additional 10 cases of CFS and 9 cases of PVFS within the past two years. With 3 of the cases describing both CFS/ME and PVFS, a total of eight cases of CFS/ME and post viral fatigue syndrome were included within the Observed / Expected Analyses with reaction onset dates occurring within the defined time period (section 5). During September 2010 to August 2011 there were 5 cases of CFS reported in girls aged 12-13 years (Figure 3). There were 3 cases reported during September 2011 and May 2012 (Figure 4). No signals were observed for any of the reporting levels.

CFS is a fairly common condition that can occur naturally among adolescent girls. It is estimated that 250,000 people in Britain are affected by CFS<sup>33</sup>. There is no diagnostic laboratory test or biomarker for CFS and it is often diagnosed when other possible diagnoses have been excluded. A recent study<sup>34</sup> in children aged 11 to 16 years (n=2855) enrolled in three English state secondary schools (two mixed gender and one girls-only) found that 1% of enrolled children (28 of 2855 pupils) missed  $\geq 20\%$  of school because of CFS. The study was conducted prior to initiation of the HPV immunisation programme from September 2007 to February 2008 and therefore provides evidence of CFS occurrence in adolescents in the absence of HPV vaccination. CFS will continue to be closely monitored.

### **CPRD Study**

The MHRA recently conducted a study using the CPRD (section 6). The first aim of this study was to investigate the potential association between HPV vaccination and the occurrence of fatigue syndrome in females in the UK with an ecological study that described trends in the recording of fatigue diagnoses in 12 to 20 years old girls in the CPRD before and after the introduction of the vaccination campaign. The ecological analysis showed no difference in the incidence of fatigue syndrome in girls aged 12-20 years in 2009-2011 compared to the years immediately before the introduction of the HPV vaccination (2006-2007). A trend was observed of decreasing diagnosis in the earlier years 2003-2005 and a similar pattern was seen in adults aged 21+ years. However, in boys aged 12-20 this trend was seen to continue with a further decrease in diagnosis in 2009-2011 compared to 2006-2007. The ecological analysis does not suggest the possibility of a large increased risk but it does indicate a need for further controlled analyses.

The second part of the study was a self-controlled case series (SCCS) study that investigated the temporal relationship between HPV vaccination and fatigue diagnoses in females in the CPRD. As with any similar type of study, the SCCS could not rule out an increased risk of fatigue syndrome with HPV vaccination, mainly to the high level of missing exposure data with

<sup>33</sup> <http://www.meassociation.org.uk/?p=1001>

<sup>34</sup> Crawley EM *et al.* Unidentified Chronic Fatigue Syndrome/myalgic encephalomyelitis (CFS/ME) is a major cause of school absence: surveillance outcomes from school-based clinics. *BMJ Open* 2011;**1**(2):e000252

only 30-40% of girls having a record of HPV vaccination while the uptake rates are known to be generally >80% (section 3) and the difficult nature of the diagnosis. Overall there was no evidence of an association between HPV vaccine and fatigue syndromes based on the available data within CRPD.

### **Complex regional pain syndrome**

Up to 31<sup>st</sup> July 2012 six cases of complex regional pain syndrome have been reported. The cause of the syndrome is unknown but common predisposing conditions include trauma, infection, surgery, cervical radiculopathy, soft tissue contusions, fractures, tendon ruptures and myocardial infarction and CRPS has been associated with vaccines such as rubella and Hepatitis B vaccines. While there is a clear temporal association in the majority of cases associated with the HPV vaccine CRPS may be more likely attributed to needle trauma rather than the vaccine constituents. A 'snapshot' Observed / Expected method was used to calculate Observed / Expected ratios (section 4.3.5) and while this crude analysis is subject to limitations, the observed number of events in 12-18 year old girls administered Cervarix was found to be well below the expected number of events based on published incidence rates not restricted to 12-18 year olds. Cases of CRPS will continue to be monitored.

### **Use during pregnancy**

Cervarix is not recommended during pregnancy. During the Cervarix clinical development program, a total of 3,993 pregnancies were reported including 2,009 in women who had received Cervarix. However the proportions of pregnant subjects who experienced specific outcomes (e.g., normal infant, abnormal infants including congenital anomalies, premature birth, and spontaneous abortion) were similar between treatment groups. There have been a total of 31 ADRs reported within the Pregnancy, Puerperium and Perinatal conditions SOC (Table 5) and a further 33 ADRs reported within the Congenital, Familial and Genetic disorders SOC (Table 6). There is no clear pattern to suggest that Cervarix use during pregnancy results in a specific congenital abnormality or is associated with a high risk of spontaneous abortion. This is supported by pregnancy outcome data collated by both the Health Protection Agency (HPA) using their Vaccines in Pregnancy (VIP) registry and the UK Teratology Information Service (UKTIS). To further investigate the risk of spontaneous abortion GSK is conducting a post-marketing safety study to assess this risk during the first 23 weeks of gestation in women aged 15 to 25 years exposed to Cervarix in the UK using the CPRD. The inadvertent use of Cervarix during pregnancy will continue to be closely monitored.

## **8. CO NCLUSIONS**

Cervarix has been subject to enhanced pharmacovigilance since it was first introduced for routine use in the national HPV immunisation programme in September 2008. The need to quickly identify potential new safety signals, and to minimise the risk of coincidental events being attributed to the vaccine, was recognised prior to use. To take this forward the MHRA introduced an enhanced pharmacovigilance strategy with intensive monitoring and effective communications. Using the Observed/Expected analyses and MaxSPRT events of interest including Guillain-Barré Syndrome (GBS), encephalitis, Bell's palsy (VIIth nerve paralysis/facial palsy) and chronic fatigue syndrome / post viral fatigue syndrome were previously shown to occur at a level less than expected within the background population. Overall the enhanced pharmacovigilance strategy endorsed by the CHM has been a success.

Despite significant usage, with over 6 million doses administered in the UK, the number of suspected ADRs received by the MHRA is not unexpected with the majority recognised adverse reactions of Cervarix or psychogenic in nature and related to the vaccination procedure rather than the vaccine. Using the Observed/Expected analyses no new signal has been detected for the events of interest in the past two years. A recent CPRD study found no evidence of an association between HPV vaccine and fatigue syndromes based on the available data within CPRD. No other new signals have been identified that warrants regulatory action.

The safety experience of Cervarix up to 31<sup>st</sup> July 2012 supports the previous conclusion that the benefit/risk balance of Cervarix remains positive. As with all medicines and vaccines the safety of Cervarix will continue to be monitored by the MHRA.

## **9. ADVICE        SOUGHT**

The advice of the CHM, PEAG and BVEAG is sought on the conclusions of the report.