



## MHRA PUBLIC ASSESSMENT REPORT

### Cervarix HPV vaccine: update on UK safety experience at end of 4 years use in the HPV routine immunisation programme

December 2012

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# PLAIN-LANGUAGE SUMMARY

## Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest safety updates through several means including public assessment reports. This report summarises the safety experience in the UK with Cervarix (the human papillomavirus [HPV] vaccine), covering almost four years of its use after its introduction in September 2008.

HPV is a virus<sup>1</sup> that causes some common sexually-transmitted diseases, such as genital warts. There are many types of HPV virus; genital infection with a high-risk or oncogenic<sup>2</sup> HPV virus is the main cause of cervical<sup>3</sup> cancer, and is responsible for nearly 3000 cases of this cancer every year in the UK. HPV type 16 is responsible for almost 60% of all cervical cancers and HPV type 18 for more than 15%. A routine immunisation programme for HPV was started across the UK on 1 September 2008 for girls aged 12–13 years, including an initial catch-up programme for girls aged 17–18 years. The vaccine given was Cervarix, which protects against infection with HPV types 16 and 18. For more information on the HPV vaccine, please see our [webpage](#). By immunising<sup>4</sup> girls against HPV before they get infected, the Department of Health estimates that [up to 400 deaths from cervical cancer every year could eventually be prevented](#).

The MHRA continually monitors the safety of all medicines and vaccines. We previously reported on safety reviews of Cervarix in 2009 following the first year of use<sup>5</sup> and again in 2010 following the second year of use<sup>6</sup>. These included a review of all suspected adverse reactions (ADRs) with Cervarix reported through the [Yellow Card Scheme](#)<sup>7</sup>. Based on a review of the 2-year safety experience with Cervarix in September 2010, the [Commission on Human Medicines](#)<sup>8</sup> (CHM) concluded that no serious new risks had been identified during its extensive use in the UK over 2 years, and that the balance of benefits and risks of Cervarix remains positive.

Following a planned review of which HPV vaccine offered the best overall package, Cervarix was replaced in September 2012 in the national immunisation programme by another HPV vaccine called Gardasil ▼<sup>9</sup>. Gardasil not only protects against genital warts caused by HPV types 16 and 18 but also against HPV types 6 and 11. The MHRA has performed a comprehensive ‘end of routine use’ review of all reports of suspected ADRs with Cervarix received during the four-year period from September 2008 up to 31st July 2012. This report summarises the results and conclusions of the ‘end of use’ review.

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<sup>1</sup> A microorganism that invades living cells and causes human infections and diseases

<sup>2</sup> Potentially cancer-causing

<sup>3</sup> Of the cervix, the lower part of the uterus (womb) that is attached to the top of the vagina

<sup>4</sup> Stimulation of the body’s immune system with a vaccine that results in the body being protected against a disease

<sup>5</sup> <http://www.mhra.gov.uk/home/groups/pl-a/documents/websitesources/con059936.pdf>

<sup>6</sup> <http://www.mhra.gov.uk/home/groups/pl-p/documents/websitesources/con096797.pdf>

<sup>7</sup> Suspected adverse drug reactions to any medicine or vaccine in the UK can be reported to the MHRA through our Yellow Card Scheme ([www.yellowcard.gov.uk](http://www.yellowcard.gov.uk))

<sup>8</sup> An independent body of experts who give advice to UK government Ministers on the safety, quality and efficacy of medicines

<sup>9</sup> The inverted black triangle symbol ( ▼ ) signifies that the medicinal product is being intensively monitored by the MHRA.

When reading this report it is essential to remember that Yellow Card reports to the MHRA relate only to **suspected** ADRs. This means that cases may be true side effects but can also be coincidental events due to underlying or undiagnosed illness that would have occurred anyway in the absence of vaccination. **The information in this report therefore cannot be considered to represent a list of side effects of Cervarix, or be used to determine the frequency of their occurrence.** The known side effects of Cervarix and the frequency with which they occur are listed in the information accompanying the product<sup>1</sup>.

## Results

Over 6 million doses of Cervarix have been given in the UK since the immunisation programme started in 2008. During the immunisation programme the MHRA has received 6213 case reports describing 14,300 suspected ADRs for Cervarix (including those where the HPV vaccine brand name was not specified). The overall reporting rate for all suspected ADRs is estimated to be about 1 report per 1,000 doses administered; this is not an unexpected reporting rate for a newly marketed vaccine used within a new national immunisation programme, with such high exposure over a four-year period.

Over 55% of the reported 14,300 reactions were recognised side effects listed in the product information such as dizziness (1385 cases), headache (1128 cases), injection-site reactions (652 cases), fatigue (378 cases), malaise (499 cases), pyrexia (319 cases) / feeling hot (147 cases), nausea (1078 cases), vomiting (487 cases), abdominal pain (240 cases) pain (128 cases) and allergic reactions (63 cases). This also included 'psychogenic' reactions, which are due to fear of the injection process rather than a side effect of the vaccine itself (mainly fainting and 'panic attacks').

## Conclusions

During the course of the four years that Cervarix was in use in the HPV immunisation programme, the MHRA closely monitored safety. The 'end of routine use' review of safety data gathered to the end of July 2012 supports the conclusions of earlier reviews that the balance of its benefits and risks remains clearly positive.

As mentioned previously, from September 2012, the HPV vaccine Gardasil▼ replaced Cervarix in the national immunisation programme<sup>2,3</sup>. Gardasil▼ has been used extensively in other countries such as the United States and its safety profile is well established. Gardasil▼ not only protects against infection with HPV types 16 and 18, but it has the additional benefit of being very effective at protecting against genital warts caused by HPV types 6 and 11. As with all vaccines and medicines, the MHRA will closely monitor its safety during routine use in the UK.

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<sup>1</sup> The Summary of Product Characteristics (SPC) and the Patient Information Leaflet (PIL), which can both be viewed on the Electronic Medicines Compendium website: <http://emc.medicines.org.uk/>

<sup>2</sup> [http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH\\_131607](http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH_131607)

<sup>3</sup> Department of Health questions and answer sheet on Gardasil▼: [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_133345](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_133345)

## 1. INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest safety updates through several means including public assessment reports.

The human papillomavirus vaccine Cervarix has been used in the UK routine HPV immunisation programme for girls aged 12-13 years from September 2008. From September 2012 Cervarix was replaced with the HPV vaccine Gardasil ▼ in the routine HPV immunisation programme. This public assessment report summarises the safety experience of Cervarix within the UK national routine HPV immunisation programme from the start of its use in September 2008 up to 31<sup>st</sup> July 2012, as reviewed by the MHRA and the [Commission on Human Medicines](#)<sup>1</sup>.

## 2. BACKGROUND

### 2.1 Cervical cancer and HPV

Worldwide, more than 273 000 deaths occur from cervical cancer each year, accounting for 9% of all female cancer deaths. Increased screening activity in recent years reduced cervical cancer mortality rates in the UK by nearly 70% in 2008 (2.4 deaths per 100 000 females) compared to 30 years earlier (7.1 deaths per 100 000 females in 1979)<sup>2</sup>. However the number of patients afflicted is still high with 957 deaths from cervical cancer in 2008 in the UK, and an estimated crude rate of 3.1 deaths per 100 000 population.

Over 99% of cervical cancers are caused by human papillomavirus (HPV) infection. Of the estimated 100 types of HPV there are about 40 genital HPV types that infect the genital area<sup>3</sup>. 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>4 5</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>6</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 as well as causing other less common cancers, and 'low-risk' types, which can 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

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<sup>1</sup> An independent body of experts who give advice to UK government Ministers on the safety, quality and efficacy of medicines

<sup>2</sup> <http://info.cancerresearchuk.org/cancerstats/types/cervix/mortality/uk-cervical-cancer-mortality-statistics#source1> accessed August 2012

<sup>3</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.

<sup>4</sup> Parkin DM & Bray F. Chapter 2: The burden of HPV-related cancers. *Vaccine* 2006; **24** S3 S11-25.

<sup>5</sup> Stanley M. Prophylactic HPV vaccines: prospects for eliminating ano-genital cancer. *Br J Cancer* 2007; **96**(9): 1320-3.

<sup>6</sup> Woodman CB *et al.* The natural history of cervical HPV infection: unresolved issues. *Nat Rev Cancer* 2007; **7**(1): 11-22.

cervical cancers<sup>1</sup>. While the majority of cases of high-risk HPV infection do 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>2</sup>.

It is estimated by the Centers for Disease Control and Prevention (<http://www.cdc.gov/>) that at least 50% of all sexually active women and men are infected by genital HPV at some point in their lives<sup>3</sup>. A study of the presence 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>4</sup>, with infection more likely to occur in the 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>5</sup>.

## 2.2 HPV vaccines

In the UK there are two HPV vaccines currently licensed: Cervarix manufactured by GlaxoSmithKline (GSK) and Gardasil ▼ manufactured by Sanofi Pasteur MSD.

### **Cervarix**

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 protective antibodies is more rapid following exposure to HPV than in unvaccinated individuals, and thus the risk of diseases caused by HPV types 16 and 18 in vaccinated individuals is reduced. Since the VLPs contain no viral DNA they cannot infect cells, reproduce or cause HPV infection.

Cervarix has been licensed in over 100 countries, and since its launch tens of millions of 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>6 7</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

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<sup>1</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>2</sup> Moscicki AB *et al.* Chapter 5: Updating the natural history of HPV and anogenital cancer. *Vaccine* 2006; **24** S3 S42-51.

<sup>3</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>4</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>5</sup> Koutsky L. Epidemiology of genital human papillomavirus infection. *Am J Med* 1997; **102**(5A): 3-8.

<sup>6</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>7</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.

provides cross-protection against HPV types 31, 33 and 45, the three most common cancer-causing virus types after types 16 and 18<sup>1</sup>.

The routine Cervarix immunisation programme which started in the UK on 1 September 2008 was mainly school-based, and targeted at girls aged 12–13 years. More than 300 000 girls were immunised each year, receiving three doses of Cervarix over a 6-month period. A catch-up programme for girls aged up to 18 years was also put in place in the first three years. For more information please visit [www.immunisation.nhs.uk/Vaccines/HPV](http://www.immunisation.nhs.uk/Vaccines/HPV).

Over 6 million doses of Cervarix have been given in the UK since the immunisation programme started in 2008, up to the end of July 2012. Vaccine uptake has been very encouraging, with over 80% of all 12–13 year old girls receiving all three doses<sup>2</sup>, reflecting the importance of this immunisation programme.

### **Gardasil▼**

The other HPV vaccine marketed in the UK is Gardasil▼. In addition to protecting against HPV types 16 and 18, Gardasil▼ also protects against two extra HPV types: 6 and 11. HPV types 6 and 11 are responsible for approximately 90% of non-cancerous genital wart cases and Gardasil▼ has been demonstrated to be 99% effective at preventing genital warts caused by these HPV types<sup>3</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).

Until recently 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 has been replaced by Gardasil▼ in the national HPV immunisation programme for girls in school year 8 (aged 12-13 years). Gardasil▼ has already been used extensively in other European countries and in the US, with tens of millions people vaccinated worldwide.

## **2.3 Understanding the information contained in this report and the process of pharmacovigilance**

### **2.3.1 Yellow Card data**

One of the ways in which the MHRA monitors the safety of medicines and vaccines is through the [Yellow Card Scheme](#), to which health professionals, patients, parent, carers, members of the public, and drug or vaccine manufacturers can report a suspected adverse reaction to a medicine or vaccine. The Yellow Card Scheme underpins safety monitoring in the UK. The safety data in this report includes cases of **suspected** adverse reactions with Cervarix, which have been reported to the MHRA<sup>4</sup> through the Yellow Card Scheme

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<sup>1</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.

<sup>2</sup> <http://immunisation.dh.gov.uk/hpv-vac-uptake-jun12/>

<sup>3</sup> Barr E and Tamms G. Quadrivalent human papillomavirus vaccine. *Clin Infect Dis* 2007; 45(5): 609-7.

<sup>4</sup> Suspected adverse drug reactions to any medicine or vaccine in the UK should be reported to the MHRA through the Yellow Card Scheme ([www.yellowcard.gov.uk](http://www.yellowcard.gov.uk))

It is important to note that a report of an adverse reaction via the Yellow Card Scheme does not necessarily mean that it has been caused by the named drug or vaccine. We actively encourage reporters to send **suspected** adverse reactions; ie, the reporter does not have to be sure that the vaccine caused the reaction. A Yellow Card report is therefore not 'proof' of a side effect and reports submitted to MHRA for vaccines may therefore be true adverse reactions to the vaccine, 'psychogenic' reactions related to the process of vaccination rather than to the specific vaccine itself (eg, nervousness or anxiety about needles or vaccination); or they may be purely coincidental events that would have occurred anyway in the absence of vaccination (ie, events due to underlying medical conditions). These data are regularly reviewed to identify any possible new adverse reactions to the vaccine.

For these reasons, **this report is not a list of known or proven adverse reactions to Cervarix vaccine and must not be interpreted and used as such.** A list of the recognised adverse reactions to Cervarix is provided in the product information for healthcare professionals (Summary of Product Characteristics) and patients (Patient Information Leaflet), which can both be viewed on the Electronic Medicines Compendium website: <http://emc.medicines.org.uk>.

Although we analyse the data reported to us in the context of the number of people vaccinated, this will not allow us to determine the actual frequency at which side effects are occurring. This is because *suspected* side effects may not actually have been caused by the vaccine, and for those which may be true side effects, not all cases may be reported to us.

### **2.3.2 MHRA's Cervarix vaccine pharmacovigilance strategy**

Because clinical trials are relatively limited in size, very rare side effects might not be identified until vaccines and medicines have been used on a wide scale in large numbers of people. Cervarix vaccine is not unique in this regard and this applies to any new medicine or vaccine. The MHRA considers the safety of medicines and vaccines to be of paramount importance and this is why we have in place robust systems for monitoring safety in the post-licensing setting. The MHRA continually monitors the safety of all medicines and vaccines throughout their marketed life – this is known as pharmacovigilance.

The main objective of the pharmacovigilance process for vaccines is to identify any new risks that may emerge as the vaccines are used. Such risks could include a new side effect, an apparent change in the nature of a known side effect, identification of factors that increase the chances of having a side effect, problems related to specific batches of a vaccine, or issues related to inappropriate use of the vaccines. The MHRA takes advice from independent experts, including that of the Commission on Human Medicines (CHM<sup>1</sup>), in assessing any identified risks. We also work very closely with our European and international counterparts in such evaluations.

With any new vaccine programme, the key challenge we face in pharmacovigilance is to distinguish real side effects from background medical conditions that would have occurred regardless of vaccination. This is especially important when very large proportions of a given group in the population are vaccinated, as in the case of the HPV vaccine programme, where more than 80% of 12–13 year old girls are vaccinated (see below).

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<sup>1</sup> An independent body of experts who give advice to UK government Ministers on the safety, quality and efficacy of medicines

Inevitably, when so many girls are vaccinated over a relatively short time period, medical conditions that naturally occur in these age groups will occur in some people not long after vaccination. This in itself does not mean the vaccine was the cause and the role of the MHRA is to assess this relationship.

The key elements of the MHRA pharmacovigilance strategy for the Cervarix immunisation programme that was implemented at the start of the vaccination programme are listed below:

- Signal<sup>1</sup> evaluation and risk assessment involving the daily assessment and categorisation of all suspected new side effects (including direct follow-up with reporters where necessary in order to obtain as much clinical information as possible).
- A proactive communication plan including:
  - Writing to healthcare professionals involved in the immunisation programme to encourage use of the Yellow Card Scheme
  - Weekly online publication of a ‘Suspected adverse reaction analysis’ report which provided an ongoing and up to date assessment of all suspected ADRs cumulatively reported via the Yellow Card Scheme ([www.mhra.gov.uk/HPVvaccine](http://www.mhra.gov.uk/HPVvaccine)).
- Safety updates in [Drug Safety Update](#): a bulletin published monthly on the MHRA website that provides health professionals with information and clinical advice on the safer use of medicines and vaccines
- Using statistical tools to identify safety signals, such as:
  - Analysing Yellow card data using statistical disproportionality methods (Empirical Bayes Geometric Mean<sup>2</sup> [EBGM]) to show whether suspected side effects are being reported more than with other vaccines
  - Real-time ‘observed versus expected’ analyses of key ‘ADRs of interest’ to identify possible new risks associated with HPV vaccines. This epidemiological approach uses a statistical sequential test method, the Maximised Sequential Probability Ratio Test (MaxSPRT), to compare the number of reported cases of suspected side effects (observed) against the normal (expected) background 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 flags possible signals when the observed number of reports exceeds the expected, based on a critical value derived from the Poisson distribution. Sequential methods are needed to allow for the multiple testing that occurs with weekly surveillance.

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<sup>1</sup> An indicator or reported information suggesting that a drug or vaccine may be associated with a previously unrecognised ADR or an existing ADR that is different from current expectations

<sup>2</sup> The size of the EBGM may give some idea about the strength of evidence from case reports for a particular reaction; ie, the larger the value, the stronger the potential association between the drug and the reaction. More than three reports of a reaction, with an  $EBGM \geq 2.5$  and an  $EB05 \geq 1.8$ , is classed as a signal. EB05 and EB95 are the lower and upper bounds of the 2-sided 90% confidence intervals around the EBGM.



- For the last two academic years retrospective ‘Snapshot’ Observed / Expected analyses were also used for the ‘ADRs of interest’ (see section 3.2.1).

## **2.4 Previous assessments of safety data**

In February 2009 and again in September 2009 (1-year safety review<sup>1</sup>) 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.

In September 2010 a 2-year safety review<sup>2</sup> 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 administered 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 a fear of the injection process and not the vaccine itself (ie, ‘psychogenic’ in nature). For the cases of chronic fatigue syndrome, facial palsy, Guillain Barré Syndrome and encephalitis that were reported, the available supporting evidence and the observed versus expected analyses did not suggest that the vaccine had caused these conditions, but suggested that they may have been coincidental events. No new risks were identified in association with Cervarix despite extensive exposure in the UK. The CHM endorsed the conclusions of the safety review and agreed that the balance of risks and benefits of Cervarix remained positive.

Over 6 million doses of Cervarix have now been administered in the UK since the programme started in 2008. The HPV immunisation programme has been considered a success with uptake figures among the highest in the world<sup>3</sup>.

Since 2010 the vast majority of vaccine has been administered to girls 12-13 years of age. This is reflected in the ADR data we have received, with the majority of cases reported in females aged 12-13 years (Table 3; section 3.2).

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<sup>1</sup> <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087699>

<sup>2</sup> <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON096806>

<sup>3</sup> <http://immunisation.dh.gov.uk/annual-hpv-vaccine-coverage-in-england-in-201011-report>

### 3. UK SAFETY DATA

#### 3.1 Clinical trial and post-marketing data

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 categorised as 'very common' (may affect more than 1 in every 10 people vaccinated). Injection-site pain occurred the most frequently (after 78% of all doses). The majority of these reactions were of mild to moderate severity and were not long-lasting.

Common reactions occurring that may affect up to 1 in 10 people vaccinated include: gastrointestinal symptoms such as nausea, vomiting, diarrhoea and abdominal pain; itching/pruritus; rash; urticaria; arthralgia; and fever ( $\geq 38^{\circ}\text{C}$ ). Reactions identified within the clinical trials that may affect up to 1 in 100 people vaccinated 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 product information (the Summary of Product Characteristics and the Patient Information Leaflet).

#### 3.2 Summary of reports of suspected adverse reactions to Cervarix

All suspected adverse reactions (ADRs) reported in association with Cervarix to the MHRA through its spontaneous ADR reporting scheme, the Yellow Card Scheme (<http://yellowcard.mhra.gov.uk/>), up to 31<sup>st</sup> July 2012 were included within the review. This included UK reports received from healthcare professionals, patients, parents/carers and marketing authorisation holders (MAHs). Given that the vast majority of HPV vaccine used in the UK was 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.

From April 2008 up to 31<sup>st</sup> July 2012, the MHRA received a total of **6213 reports including 14 300 reactions**. The total number of reports considered to be serious<sup>1</sup> was 1906 which equates to 31% of the total number of ADR reports. A large majority of these reports were psychogenic in nature (due to the injection process and not due to the vaccine *per se*) and so the proportion of reports that were serious is not unexpected.

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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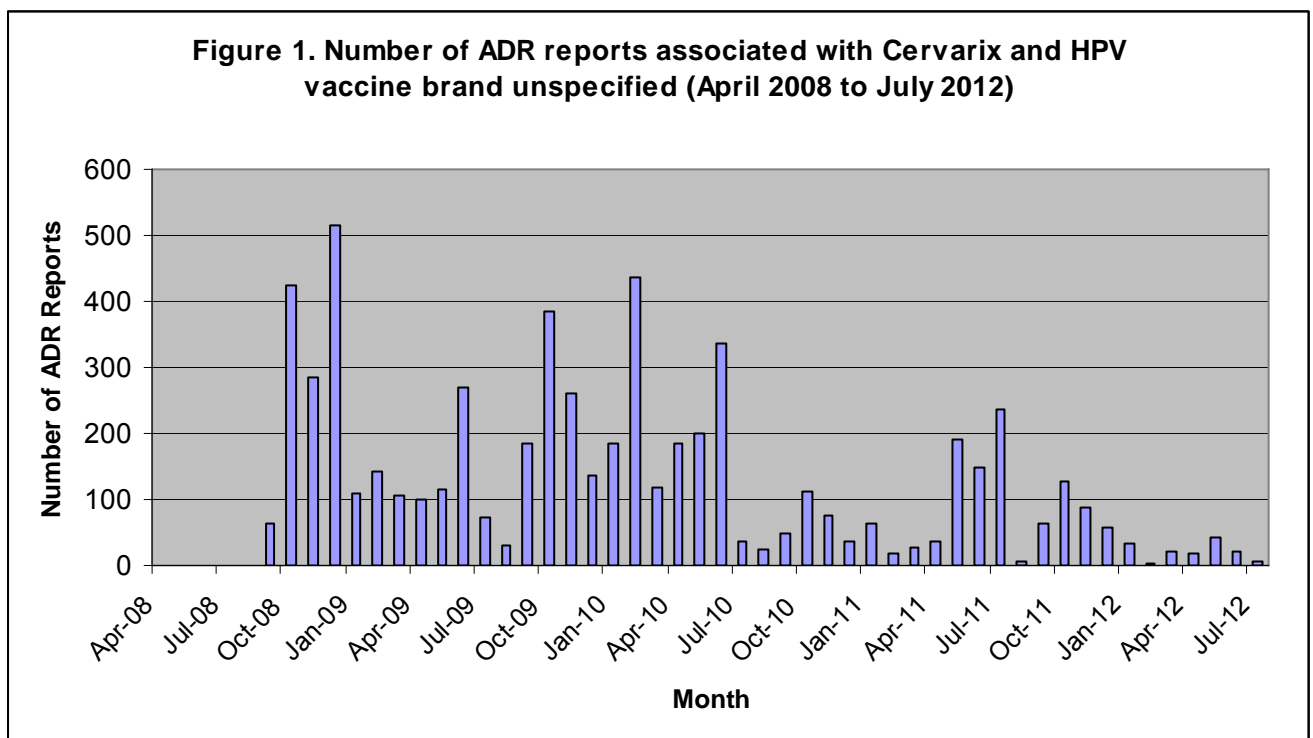
<sup>1</sup> Seriousness as defined by the Council for International Organizations of Medical Sciences (CIOMS): 'fatal, life-threatening, causing hospitalisation, resulting in persistent or significant disability or incapacity, requiring intervention to prevent permanent damage, or causing congenital anomalies' or that the reporter considered the reaction to be serious. When analysing Yellow Card data, specific 'alert terms' are also considered to be serious

**Table 1.** Total number of adverse reaction (ADR) reports associated with Cervarix and HPV vaccine brand unspecified received by the MHRA by year, from 2008 - 2012

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.



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 more than two-thirds of all reports received by the MHRA. As the main administrators of the vaccine in schools nurses were well-placed to observe and then report ADRs to the MHRA and their valuable contribution is recognised.

**Table 2.** The number and percentage of adverse reaction (ADR) reports associated with Cervarix, categorised by reporter source

Reporter type	Number of reports	Percentage of reports
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 (eg, a parent and a healthcare professional)

As expected from the typical age of the vaccine recipients, the large majority of adverse reactions were reported in those aged 12-13 years (table 3).

**Table 3.** The number and percentage of adverse reaction (ADR) reports associated with Cervarix, stratified by the age of the patient

Age	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>

When broken down by the type of reaction, it is apparent that more than half of the reported ADRs fall within three areas - nervous system disorders, general disorders and administration site conditions and gastrointestinal disorders (table 4). More detailed information on these types of reaction is presented in section 3.2.1 below.

**Table 4. Total number and percentage of adverse reactions by System Organ Class (SOC)**

<b>MedDRA System Organ Class (SOC)</b>	<b>Number 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>

MedDRA= Medical Dictionary for Regulatory Activities

The reactions in this public assessment report have been classified according to assessment by MHRA scientists using the Medical Dictionary for Regulatory Activities (MedDRA: which is used by authorities who regulate medicines, such as the MHRA).

### 3.2.1 Analysis of case reports

Individual suspected adverse reaction reports are reviewed on a continuous basis by MHRA scientists to identify whether there are any new safety signals. In addition to this routine review, age-specific and gender-specific background incidence rates for a range of 'events of interest' associated with Cervarix were also calculated on a weekly basis using 10 years of historical data from the former General Practice Research Database (GPRD; now known as the Clinical Practice Research Datalink<sup>1</sup> [CPRD]). Incidence rates were used to estimate the 'expected' number of reports on a continuous cumulative basis. Cases of suspected adverse reactions received formed the 'observed' number of reports. Using these two numbers an 'observed versus expected' analysis using a signal generation tool called the statistical sequential test method, or the MaxSPRT, helped to determine the proportion of these events that would have occurred in the absence of vaccination in the age-group receiving Cervarix.

Retrospective 'Snapshot' Observed/Expected analyses were also conducted for the 'events of interest' including Guillain-Barré syndrome, Bell's/ facial palsy, chronic fatigue syndrome/post viral fatigue syndrome, complex regional pain syndrome and encephalitis for the academic years 2010/11 and 2011/12. More information on the outcome of these analyses is provided below.

Data on the number of girls vaccinated was available to MHRA 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 'snapshot' statistical analyses if the reaction onset date was between these dates.

#### **Reports with a fatal outcome**

There have been two cases with a fatal outcome reported to MHRA in temporal association with Cervarix since its licensing in 2008. Both these cases have already been described in the 2-year safety review published on the website in October 2010<sup>2</sup>.

These were tragic cases and our sympathies are with the families; however, there was no indication that Cervarix caused or contributed to the unfortunate fatal events. A post-mortem for the first case found that a malignant tumour affecting the girl's heart and lungs

<sup>1</sup> <http://www.cprd.com/intro.asp>

<sup>2</sup> <http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con096797.pdf>

was the cause of her death and the vaccine did not play a role. The second case was due to underlying infection with group A streptococcal septicaemia. No additional cases with fatal outcomes have been reported since the period of the review.

### ***Nervous system disorders***

The 'nervous system disorders' System Organ Class (SOC) contained the greatest number of reports (4263; 30% of the total) of suspected ADRs. Within this SOC, the highest numbers of suspected adverse reactions relate to headache (1128), dizziness (1367), syncope (faints) (501), hypoaesthesia (251), paraesthesia (148) and tremor (110). These symptoms are very often a consequence of a 'psychogenic' response, whereby the fear or anticipation of a needle injection can trigger a faint or a mild 'panic attack'. These reactions or related terms are included within the product information as possible side effects of the vaccination process (not to Cervarix specifically), and can occur with any injection. 'Psychogenic reactions' can also manifest as loss of consciousness/altered state of consciousness, vision disturbance, 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 also been added to the Cervarix Summary of Product Characteristics (SPC) given that the population vaccinated is particularly prone to this type of reaction.

Within the 2-year review 2236 adverse reactions (21% of the total), were classified as 'psychogenic' reactions.

Other events of interest within this SOC include Guillain-Barré Syndrome, encephalitis and Bell's palsy (VIIth nerve paralysis/facial palsy), convulsions and complex regional pain syndrome; these are described in more detail below.

#### *Guillain-Barré Syndrome*

A total of five reports of Guillain-Barre syndrome (GBS) have been received, all previously reported in the 2010 2-year review.

All five cases of GBS were included in the Observed/Expected analysis using the MaxSPRT test method (see section 2.3.2, pg 8 of this report for details). Two reports 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 number of cases is consistent with chance and there was no evidence of a safety signal for GBS.

The absence of additional reports 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.

#### *Encephalitis*

A total of six reports of encephalitis and one report of encephalitis lethargica have been received, five of which were previously reported in the 2010 2-year review and suggested that this was consistent with chance<sup>1</sup>. One further report of encephalitis has been received since September 2010 which does not affect that above conclusion.

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<sup>1</sup> <http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con096797.pdf>

There is insufficient evidence to suggest a causal association between Cervarix and encephalitis.

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

A total of nine cases of Bell's palsy (VIIth nerve paralysis/Facial palsy) have been reported, six of which were previously discussed in the 2010 2-year review<sup>1</sup>. Of these six cases, two were included in the first year's MaxSPRT analysis and four in the second year's analysis. The results for both years did not indicate an association between Cervarix vaccine and facial palsy.

There were two reports of Bell's palsy/VIIth nerve paralysis reported that occurred during the period 2011-2012. The observed number of cases did not exceed the expected number. No cases were reported during 2010-2011.

Reported cases of Bell's palsy are consistent with chance and there is no evidence of a causal association with Cervarix.

#### *Convulsions*

There were 97 reports of seizures and seizure disorders reported, including convulsion (74), grand mal convulsion (11), clonic convulsion (1) and other reactions.

During a fainting episode (as a psychogenic response to the needle injection), a person's limbs can jerk during recovery, and these tonic-clonic movements are often reported as a seizure or convulsion. The majority of reports of convulsion were associated with reactions such as loss of consciousness/syncope or with additional conditions. Tonic clonic movements, in the context of psychogenic events associated with syncope, are listed in the SPC.

There is insufficient evidence to suggest a causal association between Cervarix and convulsion or seizure.

#### *Complex regional pain syndrome*

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.

There were six suspected cases of CRPS reported in association with Cervarix.

While there is a temporal association in the majority of cases associated with the HPV vaccine CRPS may be attributed to needle trauma, as proposed by Genc *et al.*, 2005<sup>1</sup>, rather than the vaccine constituents. It is also possible that such reports were coincidental.

The 'snapshot' Observed/Expected method was used for analysis using incidence rates 26.2 per 100,000 person years<sup>1</sup> and 5.46 per 100,000 person years<sup>2</sup> as reported in the

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<sup>1</sup> Genc H *et al.* Complex regional pain syndrome type-I after rubella vaccine. *Eur J Pain* 2005; **9**(5): 517-520.



literature. 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% confidence interval [CI] 0.01-0.07) and 0.16 (95% CI 0.06-0.35) respectively. This indicates that the reported events are well below the natural incidence in 12-18 year old girls who have received Cervarix.

Reported cases of CRPS are consistent with chance and there is insufficient evidence of a causal association with Cervarix

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

This SOC contained the second highest number of reactions reported (2940 ADRs; 20.56%). The vast majority of these reports related to injection site reactions (652), fatigue (378), malaise (499), pyrexia (319)/feeling hot (147), peripheral oedema (229) and pain (128). The majority of these reactions are listed in the product information.

Other events of interest in this category include chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME)

#### *Chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) and post viral fatigue syndrome*

Chronic Fatigue Syndrome (CFS) is a naturally occurring condition that occurs naturally amongst adolescents and is diagnosed when other possible conditions have been excluded.

At the time of the 2-year 2010 review (up to 28<sup>th</sup> July 2010)<sup>3</sup> the MHRA had received four reports of CFS and six reports of post-viral fatigue syndrome. Results of the MaxSPRT analysis for both 2008-2009 and 2009-2010 suggested that the reports were consistent with chance and this was supported by the lack of consistent temporal association and clinical characteristics of the reports of CFS/ME. From 2010–2012, the MHRA received an additional 10 reports of CFS.

From September 2010 to August 2011 there were five reports of CFS in girls aged 12-13 years. The observed number of cases did not exceed the expected number (figures 2a and 2b). Reported cases of CFS/ME are consistent with chance and there is no evidence of a causal association with Cervarix.

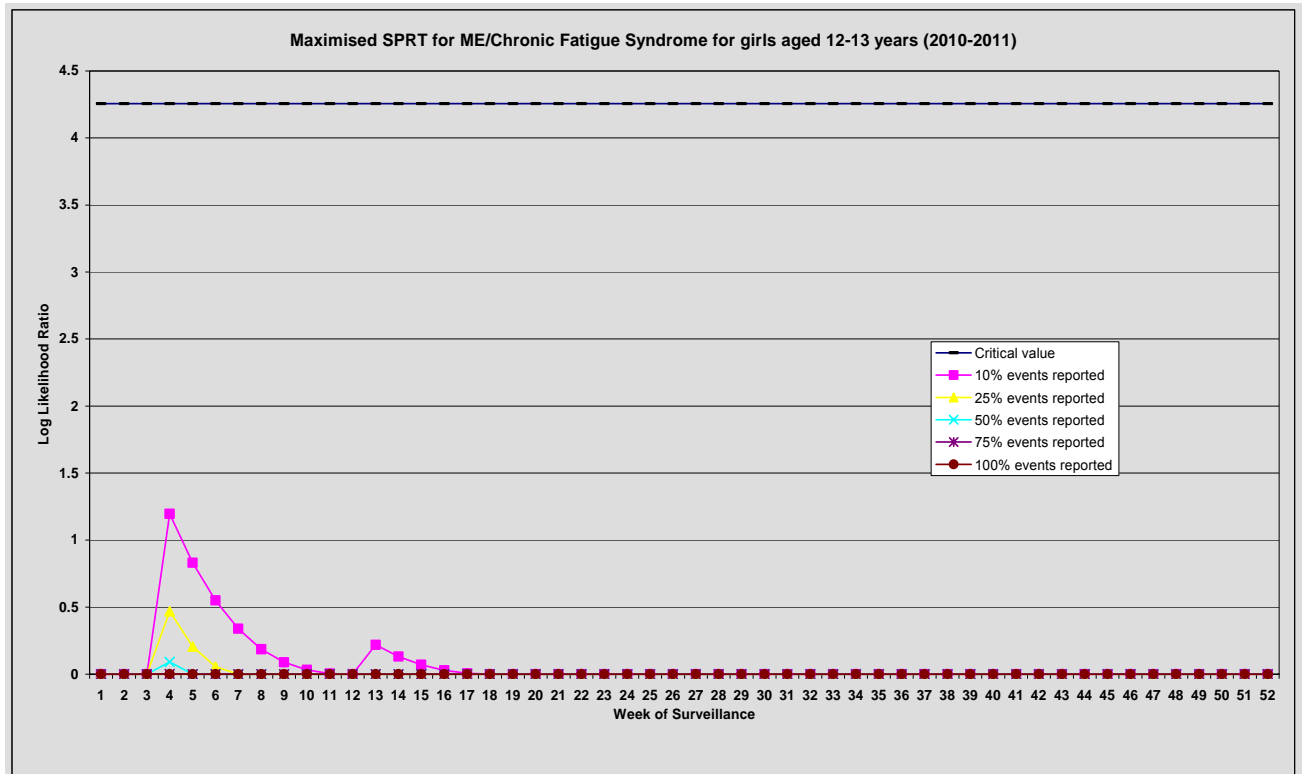
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<sup>1</sup> De Mos M *et al.* The incidence of complex regional pain syndrome: a population-based study. *Pain* 2007; **129**(1-2):12-20.

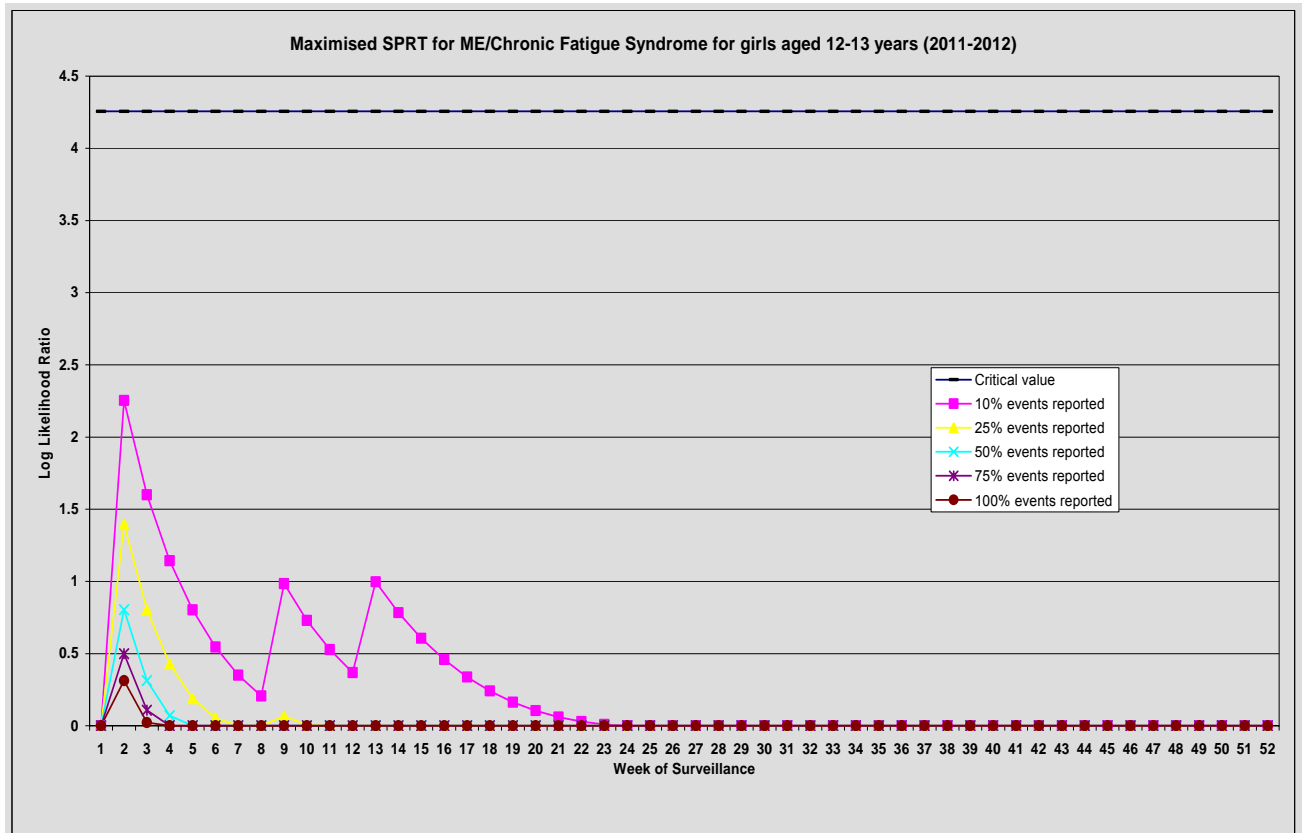
<sup>2</sup> Sandroni P *et al.* Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. *Pain* 2003;**103**(1-2):199-207.

<sup>3</sup> <http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con096797.pdf>

**Figure 2a** The Maximised Sequential Probability Ratio Test (MaxSPRT) for reports of myalgic encephalomyelitis (ME) or chronic fatigue syndrome (CFS) with Cervarix during 2010 - 2011



**Figure 2b** The Maximised Sequential Probability Ratio Test (MaxSPRT) for reports of myalgic encephalomyelitis (ME) or chronic fatigue syndrome (CFS) with Cervarix during 2011 – 2012



An ecological study and a self-controlled case series study using the Clinical Practice Research Datalink (CPRD; link to <http://www.cprd.com/intro.asp>) performed by MHRA in 2012 did not find an increased risk of fatigue syndromes with Cervarix. The results from these studies are being submitted for publication in a peer-reviewed journal.

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

The Brighton collaboration case definition of anaphylaxis for all levels of diagnostic certainty requires diagnosis to be supported by clinical features of sudden onset with rapid progression and include signs and symptoms involving multiple (at least two) organ systems including dermatological, cardiovascular and respiratory features.

There were 123 case reports included in the immune system disorders category, of which 63 were reported as an anaphylactic/anaphylactoid reaction. In the 2-year 2010 review 47 cases of anaphylaxis/anaphylactoid reactions were reported with the majority of reports containing insufficient details to suggest true anaphylaxis as defined by the Brighton criteria<sup>1</sup>.

<sup>1</sup> Cases of suspected anaphylaxis are assessed against the Brighton Collaboration case definition – a standardised set of case definitions of adverse events following immunisation ([www.brightoncollaboration.org](http://www.brightoncollaboration.org)) used to determine whether the case is indeed likely to be anaphylaxis.

Even if we make a conservative assumption that all reports are true anaphylaxis, a reporting rate of 63 cases per 6 000 000 doses administered would be consistent with general estimates of vaccine-induced anaphylaxis. Allergic reactions including anaphylactic and anaphylactoid reactions are listed in the product information and patients known to be hypersensitive to the active substance or the excipients of Cervarix vaccine are contraindicated from administration of this vaccine.

### ***Neoplasms***

Nine reports were included in the neoplasms category (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). These include the case with a fatal outcome, which has been discussed previously (see 'Reports with a fatal outcome', pg 14. There is no clear pattern in these cases to suggest that Cervarix is associated with an increased neoplastic risk.

### ***Safety in pregnancy***

Cervarix is not recommended during pregnancy. During the Cervarix clinical development program the proportion of pregnant subjects for whom the outcome of pregnancy was known (eg, normal infant, abnormal infants including congenital anomalies, premature birth, and spontaneous abortion) were similar between the study group that received Cervarix, and the control group. Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development.

There is no indication that being vaccinated with Cervarix during pregnancy results in any congenital abnormality or is associated with a risk of spontaneous abortion (or miscarriage) or other adverse pregnancy outcomes.

## 4. DISCUSSION

In September 2008 Cervarix was introduced in the UK for the prevention of premalignant cervical lesions and cervical cancer due to HPV in female adolescents in a national HPV immunisation programme. HPV vaccination is eventually expected to prevent up to 400 deaths due to cervical cancer each year in the UK. Since Cervarix was introduced, its safety has been actively monitored by the MHRA through an enhanced pharmacovigilance strategy.

It is estimated that over 6 million doses of Cervarix have been administered in the UK since being licensed in 2007. During the first three years of the programme there was greater usage of the vaccine, with a catch-up campaign for older girls aged 13-18 years of age in addition to girls aged 12-13 years. More recently the vast majority of vaccine is administered to girls aged 12-13 years of age. 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 1-year<sup>1</sup> and 2-year<sup>2</sup> reviews of the safety of Cervarix have been published on the MHRA website and concluded that the balance of benefits and risks of the HPV vaccine were positive.

With the switch from Cervarix to Gardasil▼ within the routine HPV immunisation programme from September 2012, this report summarises the overall safety experience of Cervarix in the UK over the four year period of its use and includes consideration of usage data, suspected ADRs received through the Yellow Card Scheme and a review of events of interest using Observed/Expected analyses.

Since Cervarix was first licensed in the UK in 2007, up to 31<sup>st</sup> July 2012 the MHRA received a total of 6213 reports of suspected adverse reactions (ADRs), which included 14 300 events terms (terms which are used to precisely identify and categorise an ADR), of which almost 70% were classed as non-serious. 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 and this pattern is typical for a newly introduced medicine or vaccine. 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<sup>3</sup>. The proportion of serious reports is not unexpected given that a large majority of these reports were considered to be psychogenic in nature<sup>4</sup>. The SPC already warns about psychogenic responses to Cervarix vaccination as adolescent girls are particularly prone to these events.

Since being licensed, there have been two reports with fatal outcomes associated with Cervarix and both of these were presented previously in the 2-year review published in October 2010<sup>5</sup>. There was no indication that the vaccine caused or contributed to the

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<sup>1</sup> <http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con059936.pdf>

<sup>2</sup> <http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con096797.pdf>

<sup>3</sup> A serious reaction includes those that are fatal, life-threatening, disabling or incapacitating, resulted in or prolonged hospitalisation, congenital anomalies or considered to be medically significant

<sup>4</sup> Caused by a fear of the injection process and not due to the vaccine *per se* (mainly due to fainting, which is defined as serious in the MHRA's medical dictionary).

<sup>5</sup> <http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con096797.pdf>

*Streptococcal* sepsis or malignant neoplasm that were reported to be the cause of death in these cases.

The greatest number of suspected ADRs that were reported in association with Cervarix were classified as nervous system disorders (n=4263, 29.8%), with fainting being the most common of these. The majority of these reactions are already listed in the SPC or, like fainting, are considered to be psychogenic events based on signs/symptoms of a fear or anticipatory response to the needle injection and not a reaction to Cervarix per se. Information on psychogenic reactions is also provided in the SPC.

As part of the MHRA's enhanced pharmacovigilance strategy for Cervarix, certain events were evaluated via statistical Observed/Expected analyses, including Guillain-Barré Syndrome (GBS), encephalitis, Bell's palsy (VIIth nerve paralysis/facial palsy), complex regional pain syndrome and chronic fatigue syndrome / post viral fatigue syndrome. The available evidence suggests that the number of reports received by the MHRA of these events was no greater than expected and therefore consistent with chance, given the number of girls vaccinated and the natural incidence of these conditions in adolescent girls.

#### **Use during pregnancy**

There is no evidence to suggest that inadvertent receipt of Cervarix during pregnancy resulted in any harm to the baby or any adverse effect on the pregnancy, including spontaneous abortion (miscarriage).

## **5. CONCLUSIONS**

To date, the majority of suspected adverse reactions reported to the MHRA in association with Cervarix vaccine have related either to: side effects that are already described in the product information; the injection process and not the vaccine (ie 'psychogenic' in nature); or to events that occur commonly in the population receiving the vaccine (adolescent females).

More in-depth statistical analyses have been conducted for Guillain-Barré Syndrome (GBS), encephalitis, Bell's palsy (VIIth nerve paralysis/facial palsy), complex regional pain syndrome and chronic fatigue syndrome/post viral fatigue and there is no evidence to suggest that any of these conditions may be a side effect of Cervarix vaccine. The number of reports of these events was consistent with chance, given the number of girls vaccinated and the natural incidence of these conditions in adolescent girls.

Despite significant usage, with over 6 million doses administered in the UK, the number and nature of suspected ADRs received by the MHRA to date is very much in line with expectations.

The safety experience of Cervarix during its routine use in the four year HPV vaccination programme up to 31<sup>st</sup> July 2012 supports the previous conclusion that the benefit/risk balance of Cervarix remains clearly positive.

From September 2012, the HPV vaccine Gardasil▼ has replaced Cervarix in the national immunisation programme<sup>11</sup>. Gardasil▼ has been used extensively in other countries such

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<sup>1</sup> [http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH\\_131607](http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH_131607)

as the United States and its safety profile is well established. As with all vaccines and medicines, the MHRA will closely monitor its safety during routine use in the UK.

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<sup>1</sup> Department of Health questions and answer sheet on Gardasil ▼ :  
[http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_133345](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_133345)

## GLOSSARY

### **Allergic reaction**

The body's response to sensing a foreign substance (such as a vaccine), which can consist of symptoms such as a rash, itchy skin or breathing difficulties

### **Anaphylaxis**

A life-threatening **allergic reaction**, consisting of swelling around the mouth or eyes, and difficulties in breathing or swallowing

### **Angioedema**

An **allergic reaction** consisting of swelling beneath the skin

### **Arthralgia**

Severe pain in a joint

### **Bell's palsy**

Paralysis or weakness on one side of the face

### **Cervical cancer**

Cancer of the cervix (the entrance to the womb [uterus])

### **Chronic fatigue syndrome**

A complex disorder characterised by extreme **fatigue** and exhaustion, with other accompanying symptoms such as memory loss, sore throat, and unexplained muscle pain. Also known as myalgic encephalomyelitis

### **Clinical study/trial**

A research study that tests the effectiveness and safety of medicines in humans

### **Complex regional pain syndrome (CRPS)**

CRPS is a condition of unknown cause characterised by severe pain, swelling and changes in the skin temperature and colour of the arms and legs.

### **Connective tissue**

A type of tissue in the body made up of fibres, that provides a supportive framework for other bodily tissues and organs

### **Control group**

In a clinical trial or research study, this refers to a group of participants who receive either a **placebo** or no treatment at all, for comparison with a group who receive an **active treatment**

### **Convulsion**

Intense, involuntary muscular contractions

### **Facial palsy**

See **Bell's palsy**

### **Fatigue**

Mental or physical tiredness

### **Gastrointestinal**

Related to the stomach and intestines



**Guillain-Barré syndrome**

A disorder characterised by paralysis and loss of reflexes in the body (without a fever), usually starting in the legs. It can sometimes follow events such as vaccinations, and is thought to be caused by an immune response

**Human papillomavirus**

A group of viruses, including ones that can cause warts. Some types are associated with tumours of the genital tract, notably cervical cancer

**Hypoaesthesia**

A loss of sensitivity in the skin to feeling touch or pain

**Immunisation**

See **vaccination**

**Insomnia**

Inability to fall asleep or remain asleep for an adequate length of time

**Labyrinth disorder**

Inflammation and swelling of the inner ear area, which leads to dizziness

**Lymphadenopathy**

Enlarged lymph nodes usually associated with disease. Lymph nodes are small structures located along the lymphatic system in the neck, armpit and groin, which filter bacteria and foreign particles out of lymph (fluid derived from body tissues that circulates in the body's lymphatic system)

**Malaise**

A feeling of fatigue and bodily discomfort

**Mediastinal**

Contained in the chest cavity

**Metabolism**

The chemical processes that occur in the body in order to maintain life. These involve either breaking down substances or making new ones

**Miscarriage**

Spontaneous loss of a fetus before 24 weeks of pregnancy

**Musculoskeletal**

Relating to or involving the muscles and skeleton

**Myalgia**

Muscle pain

**Myalgic encephalomyelitis**

See **chronic fatigue syndrome**

**Nausea**

Feeling of sickness or an urge to vomit

**Oncogenic**

Tending to cause or give rise to tumours

**Panic attack**

An episode of intense fear that develops for no reason, which can trigger severe physical reactions such as rapid heart rate, sweating and shortness of breath

**Paraesthesia**

Abnormal skin sensations, such as tickling, itching or burning, usually associated with peripheral nerve damage

**Pathogen**

An agent that causes disease, such as bacteria or fungus

**Perinatal**

The period immediately before and after birth

**Pharmacovigilance**

A process or system for monitoring the safety of medicines and vaccines

**Photophobia**

Abnormal sensitivity to, or intolerance of, light

**Placebo**

Inactive dummy treatment given in a **clinical trial** to a particular patient group so their responses can be compared with the group receiving the test medicine

**Post viral fatigue syndrome**

A state of fatigue resulting from a viral infection. It is also known as **myalgic encephalomyelitis** or **chronic fatigue syndrome**

**Pre-cancerous lesions**

Abnormal or diseased change in a bodily organ or tissue

**Psychogenic**

A disorder which has a psychological, rather than a physical, origin

**Pyrexia**

Fever

**Renal**

Related to the kidney

**Respiratory**

Related to breathing

**Seizure**

Uncontrolled electrical activity in the brain which may produce a physical **convulsion**

**Streptococcal A septicaemia**

A bacterial infection in the blood caused by **pathogens** from group A family, with symptoms such as fever and exhaustion

**Subcutaneous**

Beneath the skin

**Summary of Product Characteristics**

Product information for healthcare professionals available at <http://www.medicines.org.uk/emc/>

**Syncope**

Partial or complete loss of consciousness (a faint)

**Thoracic**

Related to the chest

**Tonic-clonic**

Used to describe a type of **seizure** which has phases of both rigidity ('tonic') and rhythmic jerking ('clonic')

**Transient**

Temporary

**Vaccine**

A weakened form of a pathogen that causes a particular disease. It is introduced to the body to stimulate the body's defensive immune response, which provides protection against the disease

**Vaccination**

The injection of a **vaccine** into the body in order to stimulate the immune system, thereby preventing the disease

**Vascular**

Related to, or supplied with, blood vessels

**Vasovagal syncope**

A temporary loss of consciousness, due to a vasovagal reaction (a reduction in heart rate with a resultant drop in blood pressure that leads to fainting)

**Virus**

A sub-microscopic infectious agent that is passed from living host to living host and causes disease