



## MHRA PUBLIC ASSESSMENT REPORT

### **Cervarix (HPV vaccine): Update on UK safety covering the first two years of the HPV immunisation programme**

**October 2010**

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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 the first two years after its introduction in September 2008.

HPV is a virus<sup>a</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>b</sup> HPV virus is the main cause of cervical<sup>c</sup> cancer, and is responsible for nearly 3000 cases of this cancer every year in the UK. By immunising<sup>d</sup> girls against HPV before they get infected, [up to 400 deaths from cervical cancer every year could eventually be prevented](#). Therefore, a routine immunisation programme for HPV was started across the UK on 1 September 2008 for girls aged 12–13 years, including a catch-up programme for girls aged 17–18 years. The vaccine given is called Cervarix, which protects against infection with HPV types 16 and 18; these types cause around 70% of cervical cancer cases. For more information on the HPV vaccine, please see our [webpage](#).

As with any vaccine, the use of Cervarix may lead to adverse drug reactions<sup>e</sup> (ADRs) in some individuals. The MHRA continually monitors the safety of all medicines and vaccines and recently performed a comprehensive review of all the suspected ADRs with Cervarix reported through the MHRA [Yellow Card Scheme](#)<sup>f</sup> up to 28 July 2010, to evaluate the safety of this vaccine. This report summarises the data considered and conclusions of the review.

It is essential to remember that Yellow Card reports to the MHRA relate only to **suspected** ADRs. Therefore, cases may either be true side effects or 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 and their known frequencies are listed in the information accompanying the product<sup>g</sup>.

### Results

There were 4703 case reports of suspected ADRs for Cervarix vaccine between 14 April 2008–28 July 2010, out of at least 4.5 million doses given across the UK (around 1 report per 1000 doses). Around 17% of the reported reactions were injection-site reactions, 11% were allergic reactions and 37% were related to recognised side effects listed in the product information, such as dizziness, headache and nausea. Twenty-one per cent of the

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

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

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

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

<sup>e</sup> Side effects

<sup>f</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>g</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/>

reports were for 'psychogenic' reactions, which are due to the injection process rather than the vaccine itself. These reactions included fainting and panic attacks. The remaining reports were probably due to underlying illness rather than the vaccine.

**Conclusions and outcomes**

In September 2010, the [Commission on Human Medicines](#)<sup>a</sup> (CHM) considered the MHRA's safety review of Cervarix and concluded that no serious new risks have been identified during the extensive use of Cervarix in the UK over 2 years, and that the balance of its benefits and risks remains positive. During the course of the two years, regulatory action has been taken to ensure that the product information for Cervarix adequately reflects the very rare risk of anaphylaxis, warns that people may faint during the injection (as with any injection) and states that swollen glands under the arm may appear for a short time after vaccination. As with all vaccines, the MHRA will continue to monitor the safety of Cervarix in the UK.

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

## 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. This public assessment report summarises the safety experience in the UK with Cervarix vaccine (the human papillomavirus [HPV] vaccine), covering the first two years after its introduction in September 2008, as reviewed by the [Commission on Human Medicines<sup>a</sup>](#).

## 2. BACKGROUND

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

#### 2.1.1 Yellow Card data

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>b</sup> through the Yellow Card Scheme by healthcare professionals, members of the public and the manufacturers of the vaccine.

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). A team of scientists regularly review these data to identify any possible new adverse reactions to the vaccine.

For this reason, **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 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.

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

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

### **2.1.2 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 medicines and vaccine safety to be of paramount importance and this is why we have in place robust systems for post-licensing safety monitoring. 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, batch-related problems 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>a</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 tease out 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 85% of 12–13 year old girls are vaccinated (see below). 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. With Cervarix, we have aimed to achieve real-time analysis and transparency of the emerging data through our weekly public safety reports.

The key elements of the MHRA pharmacovigilance strategy for the Cervarix immunisation programme are listed below:

- Signal<sup>b</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

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

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

- Using statistical tools to identify signals, such as:
  - Analysing Yellow card data using disproportionality methods (Empirical Bayes Geometric Mean<sup>a</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 new epidemiological approach compares the number of reported cases of suspected side effects against the normal 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.

## 2.2 Cervarix vaccine

Cervarix is a vaccine prepared from proteins found on oncogenic HPV types 16 and 18 and highly purified virus-like particles (VLPs). The VLPs do not contain viral DNA and the vaccine cannot cause HPV infection. The vaccine also uses an 'adjuvant system' that contains monophosphoryl lipid A (MPL), a purified lipid, which enhances the response of the immune system (the system that fights diseases) to the vaccine.

When someone is given the vaccine, the immune system makes antibodies against the HPV proteins. After vaccination, the immune system is able to produce antibodies more quickly when it is exposed to the HPV viruses. The antibodies help to destroy the virus and protect against pre-cancerous lesions in the cervix and cancer of the cervix that are caused by infection with HPV types 16 or 18.

## 2.3 The Cervarix immunisation programme

The routine Cervarix immunisation programme which started on 1 September 2008 is mainly school-based, and is targeted at girls aged 12–13 years – more than 300 000 girls each year. A catch-up programme for girls aged up to 18 years has also been put in place. For more information please visit [www.immunisation.nhs.uk/Vaccines/HPV](http://www.immunisation.nhs.uk/Vaccines/HPV).

Three doses of Cervarix are given over a 6-month period at 0 (1<sup>st</sup> injection), 1 and 6 months. It is recommended that all three doses are given to provide optimal protection.

At least 4.5 million doses of Cervarix have been given in the UK as of July 2010. Vaccine uptake has been very encouraging, reflecting the importance of this vaccine programme.

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<sup>a</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.

### 3. UK SAFETY DATA

#### 3.1 Summary overview of Yellow Card reports

The last Cervarix Suspected Adverse Reaction Analysis report and Suspected Adverse Reaction Analysis for unbranded HPV vaccine report (which lists ADRs for which a brand of HPV vaccine was not specified<sup>a</sup>) can be viewed on the [MHRA website](#).

As the vast majority of 'unbranded' HPV vaccine reports were administered to girls within the age range of the routine programme, for the purpose of this assessment it is assumed that such cases were associated with Cervarix. The Cervarix data, analyses and figures below therefore relate to combined cases for Cervarix vaccine and for 'unbranded' HPV vaccine<sup>b</sup>.

From April 2008 up to 28 July 2010<sup>c</sup>, **4703 reports including 10 410 events terms<sup>d</sup>** have been reported to MHRA in association with Cervarix vaccine. The overall reporting rate is estimated to be about one report per 1000 doses.

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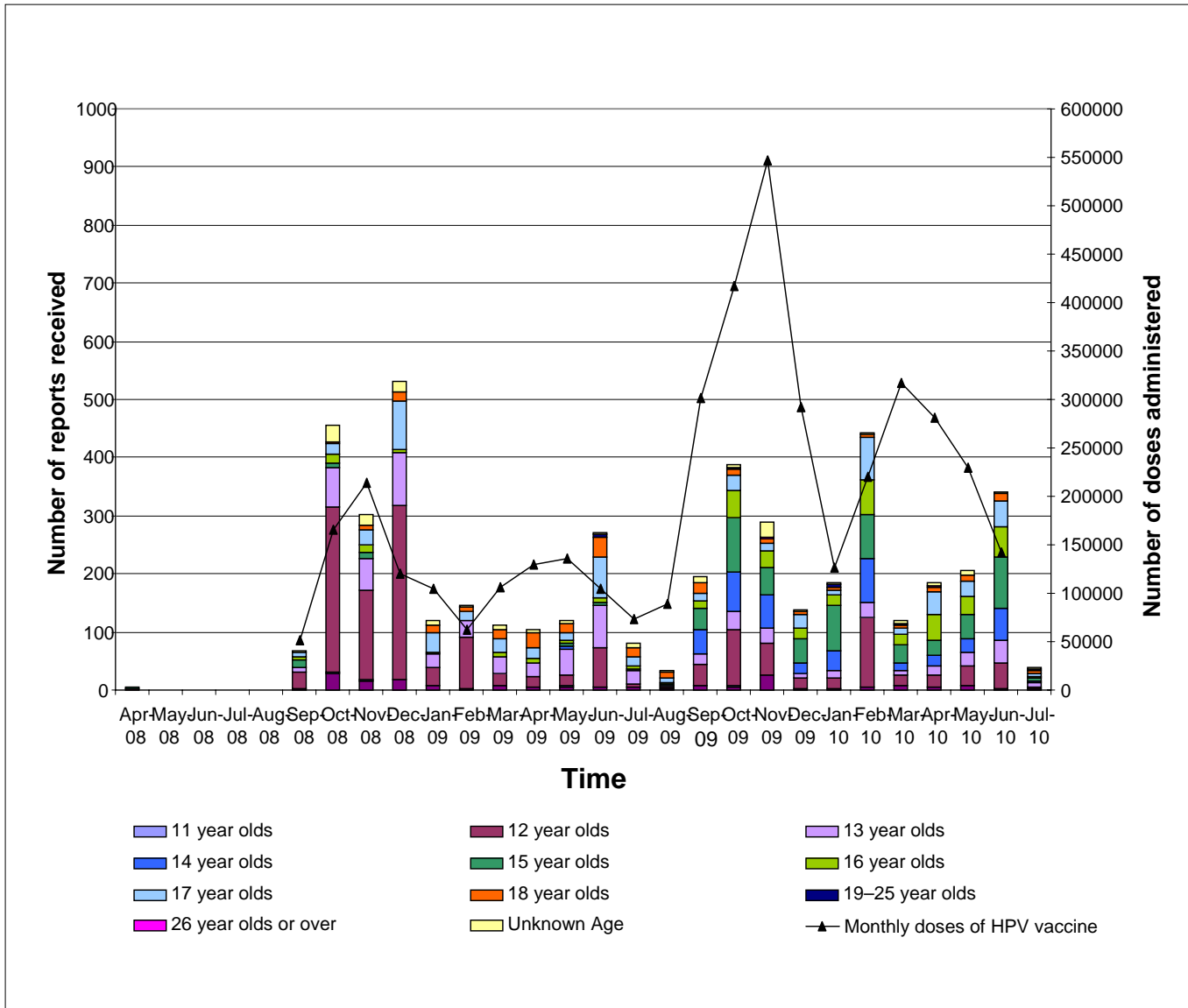
<sup>a</sup> Such reports are followed up for brand confirmation but this is not always successful.

<sup>b</sup> ADR reports for Gardasil vaccine, another brand of HPV vaccine licensed and available in the UK, are not included in this assessment as this vaccine is not used in the UK's routine immunisation programme.

<sup>c</sup> The majority of safety data have originated from the schools programme hence the cut-off date for this safety analysis after the second school year of the programme

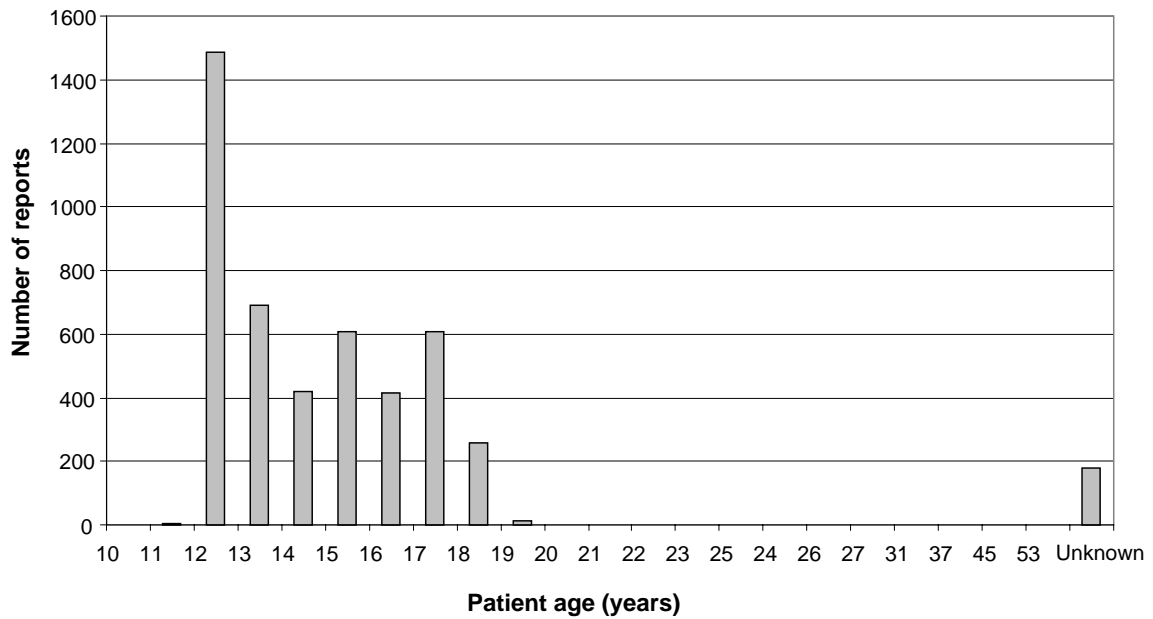
<sup>d</sup> Terms that are used to precisely identify and categorise an ADR

**Figure 1.** Number of suspected adverse reaction reports received for Cervarix vaccine from April 2008–July 2010





**Figure 2.** Number of suspected adverse reaction reports for Cervarix according to patient age



**Table 1. Source of suspected adverse drug reaction reports for Cervarix**

Reporter Qualification	Number of Reports
Nurse (mainly school nurses)	3225
Other health professional	539
GP	321
Hospital nurse	229
Consumer or other non health professional	117
Parent	102
Hospital health professional	84
Physician	80
Hospital doctor	59
Pharmacist	35
Patient	31
Carer	7
Community pharmacist	5
Hospital pharmacist	3
Unknown	3
<b>Total:</b>	<b>4840<sup>a</sup></b>

<sup>a</sup>The total number of reports per reporter shown above is greater than the overall total number of reports received, as each report may originate from more than one type of reporter.

## Discussion of summary data

At the start of the HPV programme, the MHRA anticipated receiving 3000–4,000 Yellow Cards in association with Cervarix per year, based on the number of doses being offered each year. This assumption was based on experience with previous major new immunisation campaigns (such as the initial meningitis C vaccine campaign in 1999/2000) and because the MHRA has proactively encouraged ADR reporting for Cervarix vaccine. At least 4.5 million doses had been administered by the end of July 2010, therefore the number of reports received over this time (4703) was in line with this expectation.

As expected, the vast majority of reports up to the end of July 2010 have been in girls aged 12–14 years, 15–16 years, and 17–18 years (figures 1 and 2). Also as expected, the vast majority of Yellow Card reports were submitted by nurses (mostly school nurses) (table 1).

Two suspected ADRs with a fatal outcome were reported, however one case was due to underlying infection with Streptococcal A septicaemia and the other was due to the presence of a malignant tumour in the chest (see chapter 5 for more detail). Neither case was related to the vaccination.

### 3.2 Analysis of case reports by category of adverse event

This section discusses the case reports received for Cervarix, which have also been published in public ADR summaries each week since September 2008 on the MHRA website (<http://www.mhra.gov.uk/HPVvaccine>). A suspected adverse event (AE) or adverse drug reaction (ADR) to any medicine or vaccine can be reported to the MHRA using the Yellow Card Scheme ([www.yellowcard.mhra.gov.uk](http://www.yellowcard.mhra.gov.uk)). For information on suspected adverse reactions in association with HPV vaccines received by the MHRA, see our [webpage](#).

In interpreting these reports it should be noted that the analysis is based on assessment and categorisation of **individual cases** up to the end of July 2010. 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).

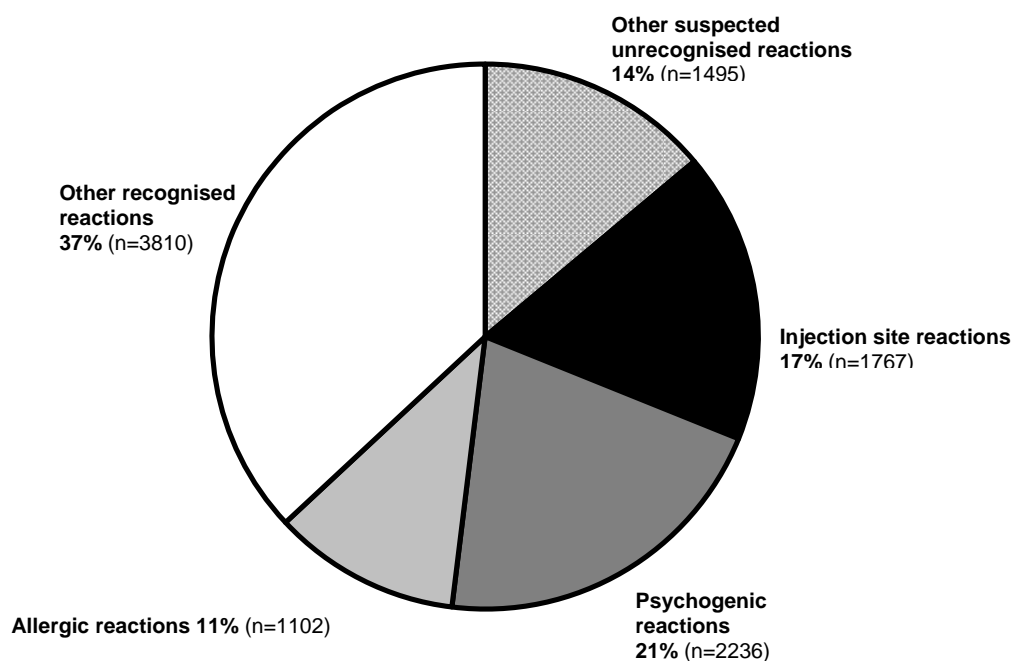
Suspected side effect reports for vaccines typically fall into one of five categories: those directly or indirectly related to the injection site ('Injection site reactions'); those that could be an allergic response to the vaccine, including skin reactions not directly related to an injection-site reaction ('Allergic reactions'); events that are due to fear or anticipation of the needle/injection ('Psychogenic events'); other known possible side effects ('Other recognised reactions'); and events following vaccination that are not a known, possible side effect to the vaccine ('Suspected adverse reactions not currently recognised').

The data are therefore presented and discussed below in the context of these categories. When assigning a specific suspected side effect report to one of these categories, a judgement is made on whether the reported event **could** possibly fit into that particular category of possible side effect/event, **not** on whether the event was actually a side effect of the vaccine. This is because, for example, even if a swollen gland (a recognised possible side effect) occurs after the vaccine, it does not necessarily mean that the vaccine definitely caused that particular case of swollen gland (it may have been due to the vaccine or it may have been due to an underlying, undiagnosed viral infection). However, most reports relating directly to the injection-site probably are due to the vaccine if no other injection was given at the site.

The same type of reaction (ie, the same MedDRA term) may appear in more than one category (eg, rash may be associated with injection site, allergic or psychogenic ADRs). However, a particular reaction from a single report or patient will appear in only one category. Also, a single report may contain more than one reaction, more than one sign or symptom of a reaction, or different reactions in several categories. Therefore the total number of cases of reactions is always greater than the total number of reports.

The majority (37%) of the total suspected ADRs reported were classified as 'recognised reactions other than psychogenic, injection site or allergic reactions', 21% were classified as psychogenic reactions, 17% as injection site reactions, 11% as allergic reactions and the remaining 14% were classified as 'other suspected reactions currently unrecognised' (Figure 3).

**Figure 3.** Proportion and category of suspected adverse reactions reported with Cervarix vaccine and HPV (unbranded) vaccine



### 3.2.1 Injection site reactions

On the basis of the clinical details contained within individual cases, 1208 reports of suspected ADRs (26% of the total report), containing 1767 event terms (17% of total reactions), were classified as injection site reactions.

Cases of injection site reactions categorised as 'pain in extremity' (n=501) were reported mainly as 'sore arm'. The cases of 'limb immobilisation' and feeling or being 'immobile' related to restricted arm or shoulder movements due to injection site pain or swelling. The cases of 'sensory loss' (n=5), 'sensation of heaviness' (n=16), 'sensory disturbance' (n=4) and 'muscular weakness' (n=6) related to symptoms including localised numbness at the

site of injection, a heavy sensation in the arm, 'pins and needles' and weakness of the injected arm, respectively. These cases were likely to be muscular, rather than neurological, in origin.

**Comment:**

As no other vaccines are given concomitantly at the same injection site, a causal association with vaccination is almost certain for most cases in this category.

Injection-site reactions such as redness, pain and swelling are recognised side effects of all vaccines, including Cervarix, and are listed in the product information. These may occur at a frequency<sup>a</sup> of more than 1 in 10 persons vaccinated. Based on the information available, there has been no apparent change in the severity or nature of injection site reactions associated with Cervarix.

**3.2.2 Allergic reactions (including anaphylaxis and skin reactions not directly related to an injection-site reaction)**

561 reports of suspected ADRs (12% of the total reports), containing 1102 event terms (11% of total reactions), were classified as allergic reactions.

Reports of anaphylaxis following vaccination often contain insufficient clinical detail to assess whether they are true cases of anaphylaxis. Also, the clinical details provided often suggest that the ADR was actually a less serious allergic reaction. For such cases, the MHRA will follow up for clinical details; however follow-up requests are not always successful. Cases of suspected anaphylaxis are assessed against the [Brighton Collaboration](#)<sup>b</sup> case definition to determine whether the case is indeed likely to be anaphylaxis, [using three levels of diagnostic certainty](#).

For Cervarix, 47 cases of suspected anaphylactic reaction were reported and, based on the clinical details, 11 cases possibly, or potentially, met at least one of the Brighton Collaboration criteria for a definition of anaphylaxis.

The remaining cases in this category related to a wide range of generalised signs and symptoms which are suggestive of a possible allergic event. These include rashes and other skin reactions that could possibly be injection site-related reactions.

**Comment:**

Due to the short onset time following vaccination for many cases, and lack of apparent/stated alternative explanation, a causal association with vaccination in such cases is possible.

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

Based on the information available, there has been no apparent change in the severity or nature of allergic reactions associated with Cervarix. However, on the basis of case

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<sup>a</sup> Based on clinical trial data

<sup>b</sup> A standardised set of case definitions of Adverse Events Following Immunization - [www.brightoncollaboration.org](http://www.brightoncollaboration.org)

reports of anaphylaxis, regulatory action was taken at the end of the first year of the immunisation programme (2009) to ensure that the product information adequately reflected the very rare risk of anaphylaxis.

### **3.2.3 Psychogenic events**

892 reports of suspected ADRs (19% of the total reports), containing 2236 event terms (21% of total reactions), were classified as 'psychogenic' reactions.

Reports are placed in this category on the basis of reported signs or symptoms and onset time suggesting a fear of, or an anticipatory response to the needle injection (ie a 'psychogenic' reaction). These are generally stated as occurring immediately or within minutes of vaccination, but can occur during, before or several hours after vaccination. Such reactions are relatively commonplace in adolescent immunisation programmes and have no lasting effects.

The most common manifestation of such episodes is syncope and symptoms of panic attack. An issue, however, is that the full range of clinical observations in addition to syncope are often also reported – this can include loss of consciousness or an altered state of consciousness, vision disturbance (including transient 'blindness'), injury, limb jerking, limb numbness or tingling, and difficulty in breathing, etc. Therefore, the reported cases which did not refer specifically to vasovagal syncope, fainting or panic attacks (eg, convulsions, visual disturbances) were concurrently reported as signs or symptoms of a psychogenic reaction. Psychogenic cases can sometimes also be misinterpreted or reported as anaphylaxis.

Many of the event terms in this category are individually listed in the product information (Summary of Product Characteristics [SPC]) as possible side effects, and several separate reports with the same event terms have been categorised as 'other recognised' reactions (eg, dizziness, nausea, headache). Such reports are placed in the psychogenic category when suggested by concurrent signs or symptoms; for instance, if immediate dizziness and nausea accompanied a syncope episode.

#### **Comment:**

It was anticipated that psychogenic events would constitute a large proportion of UK ADR reports for Cervarix. Therefore the MHRA issued a letter concerning appropriate reporting at the start of the vaccine programme. As such event reports accumulate, they could give a distorted and unrepresentative view of the safety profile (eg, the limb jerking which commonly follows a faint is often misinterpreted and reported as a seizure or convulsion, blurred vision or transient 'blindness' referring to temporary loss of vision at the start of a faint can be misinterpreted as a more serious visual or neurological condition).

It is important to realise that psychogenic events, and their associated signs and symptoms, are not actually side effects of the vaccine itself; they are due to fear or anticipation of the injection process or needle. They can also often be triggered by groups of individuals witnessing or discussing another vaccinee's 'psychogenic' event or faint.

As faints can lead to injury, it is important that procedures are in place locally to prevent any such injury. To support such local advice, regulatory action has been taken to ensure that the Cervarix product information adequately warns that people may faint during the

Cervarix injection (as with any injection) and to describe the signs and symptoms that can be associated with a fainting episode to avoid these being misinterpreted.

#### ***3.2.4 Recognised reactions other than psychogenic, allergic or injection site reactions***

This section includes ADRs recognised to be general side effects of Cervarix vaccine, which are not already included in the categories above, and are already listed in the SPC. These include a wide range of signs and symptoms similar to listed side effects, including symptoms for reported cases of 'influenza-like illness' (such as fever, myalgia and headache). Influenza-like illness is discussed further in section 5. The majority of cases of fatigue related to general tiredness which had recovered at the time of reporting. Fatigue is already listed in the Cervarix SPC.

On the basis of case reports and given the biological plausibility, regulatory action was taken at the end of the first year of the immunisation programme (2009) to include lymphadenopathy as a possible side effect in the product information for Cervarix.

There were 2053 reports (44% of the total reports), containing 3810 event terms (37% of the total reactions), which were classified as 'other recognised' reactions. These were generally non-serious and short-lasting reactions.

#### **Comment:**

As the reactions in this category, or similar signs and symptoms of these reactions, are known side effects that are listed in the product information, it is likely that many of these individual cases were causally-associated with the vaccine. However, many are also general symptoms which can be associated with unrelated underlying illnesses or infections.

In addition, it is likely that many of the cases in this category were themselves 'psychogenic' reactions (such as dizziness, nausea, and headache immediately after or within minutes of vaccination). However, as the reactions were not reported with other signs or symptoms of 'psychogenic' ADRs they were placed in the 'other recognised reactions category'.

Based on the information available, there has been no apparent change in the severity or nature of such reactions and no amendments to the Cervarix product information are required.

#### ***3.2.5 Suspected adverse reactions not currently recognised***

This section includes reports which do not fit into the four categories above. There were 734 reports (16% of the total reports), containing 1495 event terms (14% of total reactions), which were classified as 'other suspected unrecognised adverse reactions'.

Some event MedDRA terms included in this category may also be included in the above categories (eg, vomiting), but the individual case has been listed in this category if it was not consistent with currently recognised adverse reactions (eg, a case of severe or persistent vomiting).

As outlined above, MHRA scientists continually review these cases to assess whether the evidence indicates that the vaccine could be causing such conditions. This is based on

reviewing of individual cases from the UK and other countries and/or using a statistical approach (see section 2.1.1).

The key challenge is to distinguish what could be real side effects from naturally occurring, background medical conditions that would have occurred regardless of vaccination. Inevitably, when so many individuals are vaccinated over a relatively short time period, these conditions will occur in some people not long after vaccination. This in itself does not mean the vaccine was a cause and the role of the MHRA is to assess this relationship.

#### *Blood and lymphatic disorders*

In this category, there were 8 cases of blood and lymphatic system disorders reported. Aplastic anaemia, pancytopenia, neutropenia were all reported in a single case. These isolated cases of blood disorders do not currently indicate any specific safety signal.

#### *Cardiac disorders*

There were 17 cases of cardiac disorders reported, including palpitations (6); cyanosis (4); abnormal blood pressure (2); and tachycardia (2). The reported cases show no indication of any specific risks of cardiac disorders.

#### *Ear and labyrinth disorders*

17 cases of ear and labyrinth disorders were reported, including cases of ear pain (9); deafness (2) vertigo (2) and tinnitus (1). These cases were mainly associated with other signs and symptoms, and give no indication of any specific risk of ear disorders with Cervarix.

#### *Endocrine disorders*

There were two case reports of endocrine disorders, both of which were cases of acute adrenocortical insufficiency (one in a patient with Addison's disease). The cases gave no indication of any specific risk of endocrine disorders with Cervarix.

#### *Eye disorders*

There were 51 case reports of eye disorders, including blurred vision (15); impaired vision (8); photophobia (7); mydriasis (3); eye pain (3); and dry eye (1). There is no indication, from the cases of visual impairment or blurring, of any consistent clinical pattern or specific risk associated with Cervarix affecting vision.

#### *Gastrointestinal disorders*

There were 96 cases of gastrointestinal disorders reported. These included cases of nausea (28); vomiting (18); abdominal pain and discomfort (18); and diarrhoea (8). As abdominal pain is already a recognised side effect in the Cervarix SPC, these cases were included in the analysis due to their severity or association with other symptoms. The cases of gastrointestinal disorders here may represent a more severe form of a recognised gastrointestinal side effect of Cervarix, or relate to entirely coincidental gastrointestinal disorders. The available information does not indicate any specific new risks or warrant any changes to the Cervarix SPC related to gastrointestinal disorders.

#### *Infections and infestations*

There were 65 case reports categorised as 'infections and infestations', including viral infection (7); post-viral fatigue syndrome (6); lower respiratory tract infection (6); nasopharyngitis (4); herpes zoster (3); and influenza (2). These cases were most likely due to concurrent or pre-existing infections, and there is no indication from the isolated cases or clusters of any increased risk of infections with Cervarix. Post-viral fatigue syndrome is discussed further in sections 4 and 5.

#### *Injury, poisoning and procedural complications*

29 case reports were categorised as 'injury, poisoning and procedural complications', and included cases of drug exposure during pregnancy (18) and contusion (4). The cases of drug exposure during pregnancy are discussed in a later paragraph on 'reproductive system and breast disorders'. The small number of isolated cases of contusions shows no indication of any specific risks of bruising with Cervarix. It is likely that such cases were due to injection site reactions, but the reports contained little further information.

#### *Metabolic and nutrition disorders*

There were 31 case reports of metabolic or nutrition disorders, including reports of decreased appetite (9); decreased weight (6); increased blood glucose (3), and type 1 diabetes mellitus (1). Based on the information available, the small number of isolated cases showed no indication of any specific risks of metabolic disorders.

#### *Musculoskeletal and connective tissue disorders*

There were 140 case reports of musculoskeletal and connective tissue disorders, which included reports of pain in extremity (29); arthralgia (24); back pain (16); muscular weakness (14); myalgia (10) and musculoskeletal stiffness (8). Cases of arthralgia are already a recognised side effect but were included in this analysis due to the severity or persistence of symptoms being greater than would be expected of a vaccine-associated effect. As such, the cases may represent a more severe form of the recognised Cervarix side effect of arthralgia/myalgia or be associated with other reported conditions such as chronic fatigue-like illness (see discussion section below). Some of the cases of pain in the arm or the hand may have related to injection site-related reactions although this was not explicitly stated. The cases of musculoskeletal stiffness may also possibly be related to muscle pain, which is a recognised side effect in the Cervarix SPC. The available information does not indicate any specific new risks or warrant any changes to the SPC related to musculoskeletal and connective tissue disorders.

#### *Nervous system disorders*

There were 443 case reports classified as nervous system disorders, including reports of headache (58); syncope (42); dizziness (41); hypoaesthesia (36); convulsions (31); paraesthesia (26); lethargy (23); migraine (17); tremor (17); and somnolence (15).

The cases of somnolence were generally associated with transient sleepiness and fatigue following vaccination. The cases of headache, dizziness, lethargy and syncope were included in the analysis due to the severity or persistence of symptoms being greater than might be expected of a 'vaccine-associated' effect.

It is possible that the cases of hypoaesthesia and paraesthesia related to injection site-related reactions or were secondary to psychogenic events, although this was not explicitly stated. There were five case reports of Guillain-Barre syndrome and six case reports of facial palsy, which are both discussed in sections 4 and 5.

There were 50 reports of seizures (including convulsions [31], epilepsy [9] and grand mal convulsion [7]) which, based on the information available, were not necessarily related to a psychogenic ADR. Their onset ranged from immediate to 3 months after vaccination. For the suspected cases of convulsive ADRs there is currently insufficient evidence to determine an association with Cervarix. Those cases with an onset of hours to within 1 day of vaccination are highly unlikely to have been associated with the vaccine; however such cases will be kept under review. One case of convulsion was associated with encephalitis, which is discussed, along with the cases of suspected Guillain-Barre syndrome, chronic fatigue syndrome and facial palsy, in sections 4 and 5. The remaining cases of neurological disorders do not suggest any specific clinical pattern of ADRs that would indicate any causal association with Cervarix.



#### *Psychiatric disorders*

There were 57 case reports of psychiatric disorders, including insomnia (7); confusional state (6); hallucination (6); and anxiety (4). There is no indication from the isolated cases of any specific risk of psychiatric disorders. Several of these disorders can be common in adolescence.

#### *Renal and urinary disorders*

There were eight case reports of renal and urinary disorders, including urinary retention (3), urinary incontinence (2) and neurogenic bladder (1). The cases show no indication of any specific risks of renal or urinary disorders.

#### *Reproductive system and breast disorders*

There were 49 case reports of reproductive system and breast disorders; most of these related to menstrual conditions such as amenorrhoea (11) and irregular menstruation (6). Taking into consideration the common frequency of such disorders amongst the population that the vaccine is administered to (adolescents), the small number of cases did not indicate any specific new risks.

#### *Respiratory, thoracic and mediastinal disorders*

There were 75 case reports of respiratory, thoracic and mediastinal disorders, which included reports of dyspnoea (20); oropharyngeal pain (11) which related to sore throat; epistaxis (8); cough (8); asthma (7) and wheezing (5). There was no specific pattern of ADRs reported, which were mainly associated with other signs and symptoms. These cases give no indication of any specific risk of respiratory disorders.

#### *Skin and subcutaneous tissue disorders*

There were 106 case reports of skin and subcutaneous tissue disorders, which included reports of rash (13); alopecia (11); facial hypoaesthesia (8); erythema multiforme (6); and eczema (6).

There is no indication from these case reports of any specific clinical pattern or risk associated with Cervarix. Several cases may be associated with allergic or injection site ADRs although the available limited clinical details do not allow a firm conclusion. These cases do not warrant any changes to the Cervarix SPC at present.

Most of the cases related to generalised skin reactions. The cases of alopecia contained very little clinical information. There was one case of Stevens-Johnson syndrome (SJS) which was likely due to an underlying *staphylococcus aureus* infection. Given the relatively long onset time and association with fever, the cases of erythema multiforme may plausibly also have been associated with concurrent infection. The cases of facial hypoaesthesia were not associated with any neurological disorder and were possible psychogenic events.

In addition, there were also 31 case reports of vascular disorders, including 12 cases of peripheral coldness. It is possible many of these cases relate to injection site-related reactions although not clearly stated.

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

There were 234 case reports classified as general disorders and administration site conditions. These included reports of flu-like illness (40); fatigue (26); malaise (21); pyrexia (21); and chest pain (18). 'Flu-like illness' when reported as an ADR in this context with many vaccines generally refers to a non-specific range of symptoms when the patient is feeling 'generally unwell' or fatigued within 24–48 hours after vaccination. Given the range

of specific symptoms already listed that may be encompassed by 'flu-like illness' it was considered unnecessary to list this ADR in the Cervarix SPC.

Cases of chronic fatigue are discussed further below.

### **3.3 Safety in pregnancy**

There were 11 case reports of spontaneous abortion (or miscarriage). However, miscarriage in early pregnancy is very common and the reported cases are considered to be entirely coincidental. Similar reports from other countries and clinical trials indicate that no more cases of miscarriage than expected have been reported amongst pregnant females receiving the vaccine. The available information does not indicate any specific new risks or warrant any changes to the Cervarix product information.

In addition to analysing reported cases of suspected ADRs, published literature on Cervarix and pregnancy was also assessed. A pooled analysis of pregnancy outcomes in two large clinical trials with Cervarix (n=26 130; 13 075 given Cervarix, 13 055 given a control drug) has recently been published<sup>[1]</sup>. Of 3599 pregnancies that occurred during the study period, there was no significant difference in the overall estimated rate of miscarriage between the Cervarix group (around 12%) and the control group (10%). There is no indication from clinical trial data of any specific risk in pregnancy associated with Cervarix, however safety in pregnancy will continue to be closely monitored.

## 4. PROACTIVE ‘OBSERVED VERSUS EXPECTED’ ANALYSES

### **Analyses conducted for Guillain-Barre Syndrome, facial palsy, chronic fatigue syndrome, and encephalitis with Cervarix**

As part of the strategy outlined in paragraph 2.1.2, background incidence rates for a range of ‘ADRs of interest’ (calculated using 10 years of historical data from the General Practice Research Database [[GPRD](#)]) are used to estimate the expected number of reports on a continuous cumulative basis. The ‘observed versus expected’ analyses help to determine if a certain proportion of events would anyway have occurred in the age-group being vaccinated, even without the vaccination programme.

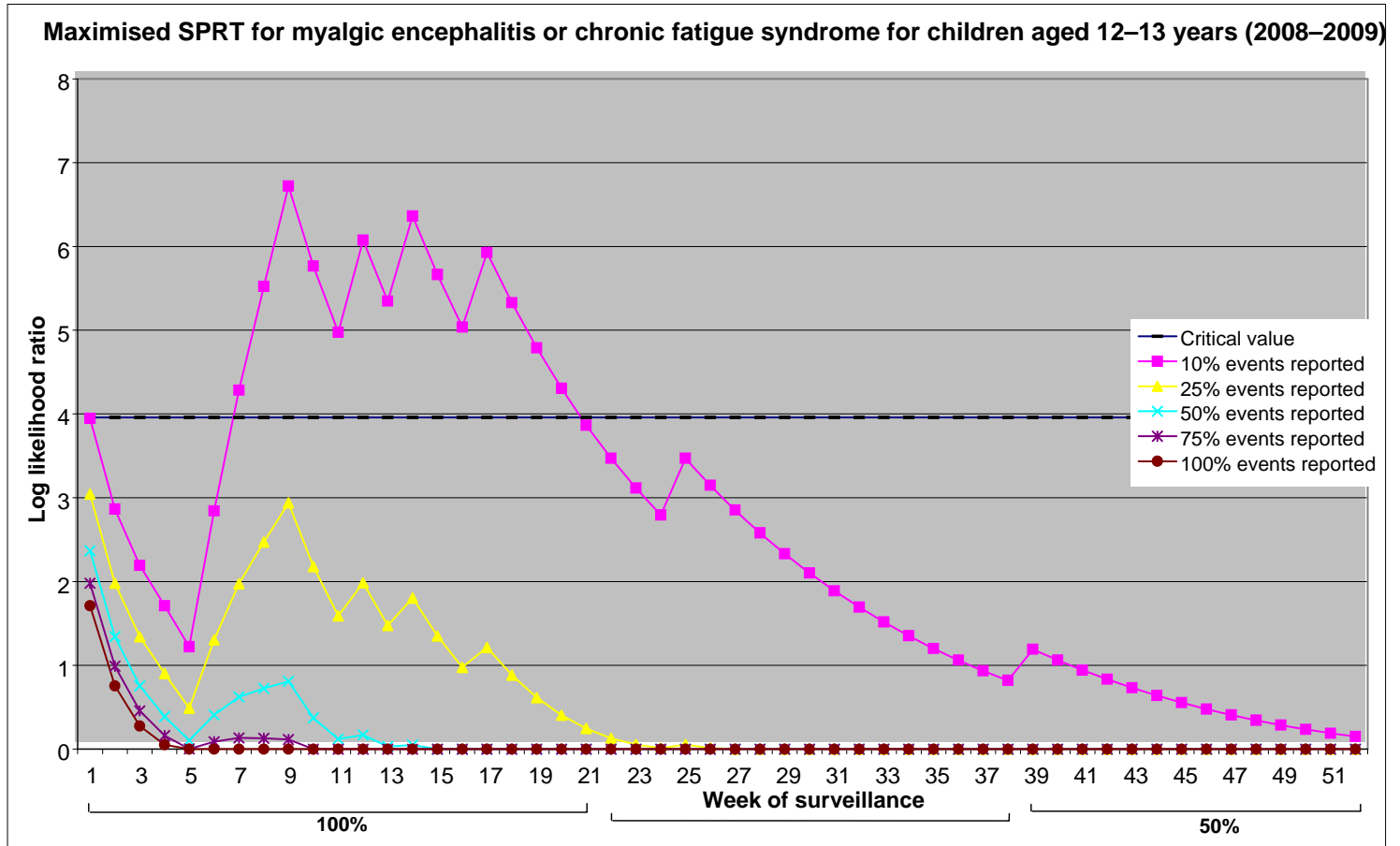
A statistical sequential test method, the Maximised Sequential Probability Ratio Test (MaxSPRT) is used to compare the observed number of reports (relative to data on vaccine usage) with the expected. ‘Observed versus expected’ analyses were conducted weekly from 2008–2010.

At the time of the data analysis (in 2010), the MHRA had received 10 reports of chronic fatigue, chronic fatigue syndrome (CFS) or post-viral fatigue syndrome (five received between 2008–2009) with Cervarix. As well as these cases of chronic fatigue or post-viral fatigue syndrome reported directly to the MHRA, we also conducted an analysis of chronic fatigue-like reports, including possible cases reported in the media (three cases). At any level of under-reporting, the observed number of cases did not exceed the expected for cases of possible CFS (see Figure 4).

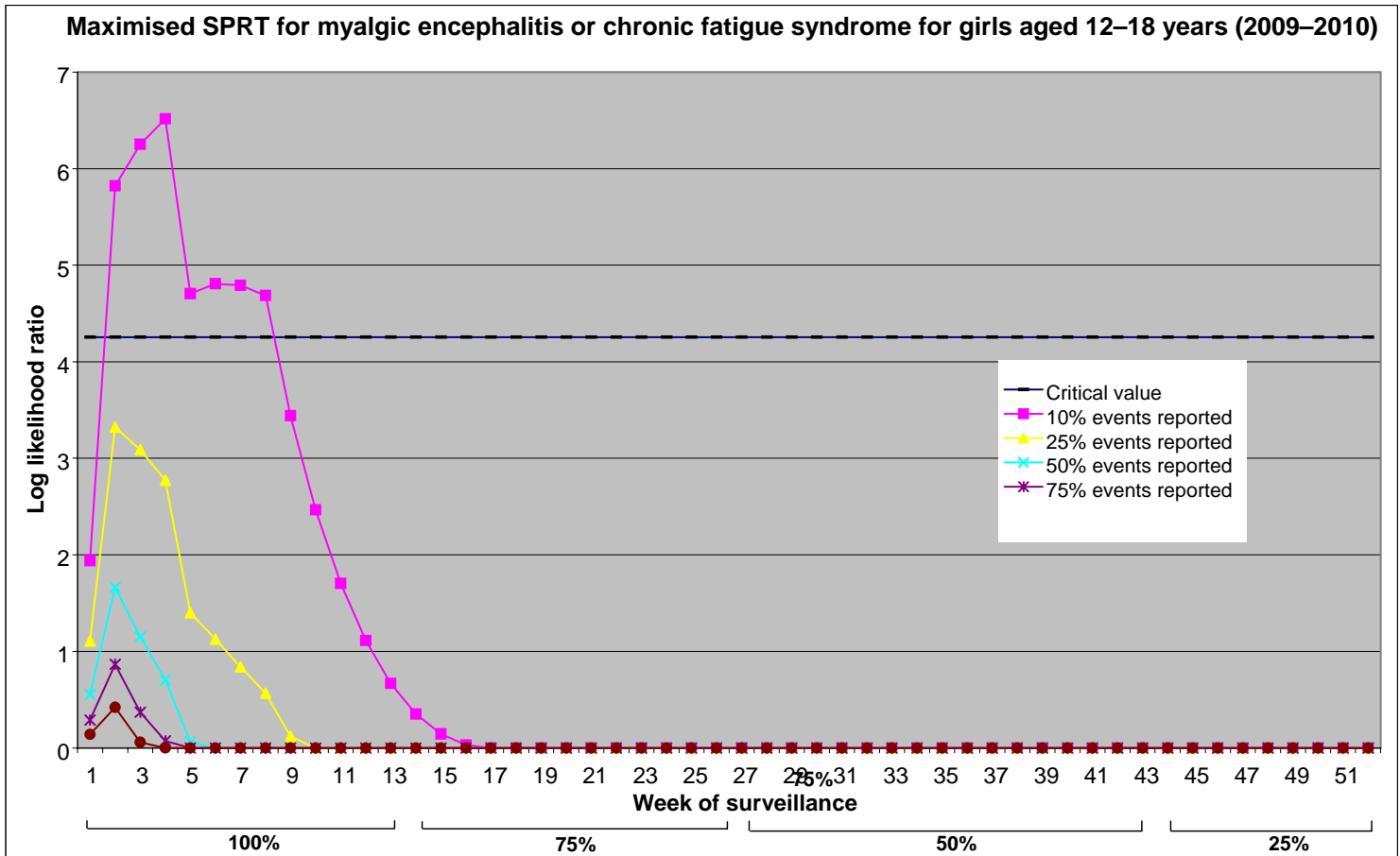
Application of the MHRA’s ‘observed versus expected’ methodology indicates that Cervarix is not associated with an apparent excess risk CFS relative to the expected background incidence of such events (ie, there is no indication from this analysis that the vaccine is a cause of this condition). Other ‘ADRs of interest’, including Guillain-Barre Syndrome, facial palsy and encephalitis were assessed using similar methods. The observed number of cases of these conditions did not exceed the expected number.

**Figure 4.** The Maximised Sequential Probability Ratio Test (MaxSPRT) for reports of myalgic encephalomyelitis (ME) or chronic fatigue syndrome (CFS) with Cervarix.

i)



ii)



## 5. FATALITY REPORTED IN THE MEDIA

Readers may have seen the media coverage in October 2009 of the young girl who died very shortly after receiving Cervarix vaccine. This was a very tragic case and our sympathies are with her family and friends. However, the post-mortem found that a malignant tumour affecting her heart and lungs was the cause of her death and the vaccine did not play a role.

Following this unfortunate incident, the MHRA initiated routine investigations into the quality of the batch administered to the girl, Cervarix vaccine batch AHPVA043BB, which were carried out by the manufacturer, GlaxoSmithKline, and two independent Official Medicines Control laboratories (the [UK National Institute for Biological Standards and Control](#) and the Belgian National Control Authority). The investigations included tests on retained samples as well as samples received from the girl's school.

The investigations revealed no evidence of any quality defect and the batch conformed to its licensed specifications. There remains no evidence to link this tragic death to administration of the Cervarix vaccine.

## 6. DISCUSSION AND CONCLUSIONS

The vast majority of suspected Cervarix ADRs reported via the Yellow Card Scheme have related either to reactions already recognised and listed in the SPC, or to 'psychogenic' ADRs which are not due to the vaccine itself, but to the injection process. This reporting profile is very much in line with the profile anticipated at the start of the immunisation programme. In addition, the total numbers of reports received via the Yellow Card Scheme were also in line with expectations at the start of the programme.

UK case reports of reactions already recognised and listed in the SPC did not indicate any change in their nature or severity that would warrant any regulatory action. Many of the reactions not previously recognised with the vaccine (section 3.2.5) related either to isolated cases or small clusters of cases for which the available information does not indicate any consistent clinical pattern that may suggest an association with Cervarix. At least 4.5 million doses were given by the end of June 2010, therefore it was inevitable that many clinical events would occur in temporal association with vaccination, regardless of a causal association, and that many of these would be reported as suspected ADRs. Such events may have been due to underlying or undiagnosed concurrent illness that was unrelated to the vaccination. Indeed, many of the case reports described signs and symptoms which may be suggestive of a concurrent infection. Given the schools-based target population and that most vaccines are given over the season of circulation of influenza-like illness and other respiratory pathogens, it is inevitable that many vaccinees will carry some form of viral illness around the time of vaccination.

### **Anaphylaxis**

Anaphylaxis is a known, rare risk of any vaccine. Although there has been no apparent change in the severity or nature of allergic reactions associated with Cervarix, on the basis of possible cases reported in the UK (regardless of diagnostic certainty), the wording 'Immune system disorders: Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema' was added to section 4.8 ('undesirable effects') of the [Cervarix SPC](#) in 2009 after an assessment of the available evidence.

### **Psychogenic events**

Although 'psychogenic events' are a well-recognised phenomenon in adolescent immunisation programmes around the world, these are not vaccine side effects itself. Nonetheless, given that such events may be associated with injury, the following wording has been included in section 4.4 ('special warnings and precautions') of the [Cervarix SPC](#): 'Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.' Many vaccine SPCs in Europe now include such a reference.

### **Lymphadenopathy**

Based on the cases reported and the plausibility of an association, lymphadenopathy was added to section 4.8 ('undesirable effects') of the [Cervarix SPC](#) in 2009 after an assessment of the available evidence.

### **Chronic fatigue syndrome (CFS)**

CFS can be a common condition amongst adolescents. It was therefore anticipated that cases of CFS would occur following vaccination, regardless of any causal association, and would be reported as suspected ADRs. A review of all the cases of CFS and chronic

fatigue-like conditions reported following Cervarix has been conducted. Most reports of possible or suspected CFS do not contain sufficient clinical details to determine or support the diagnosis of CFS, according to the [National Institute for Health and Clinical Excellence case definition of CFS](#)<sup>[2]</sup>. Amongst the number of girls vaccinated to date, at least 100 cases of CFS could have been expected by chance alone. Accounting for various levels of possible under-reporting to the Yellow Card Scheme, the number of reports submitted to MHRA (including cases reported in the UK media) from 2008–2010 is well within the range expected for normal background incidence in the vaccinated population. This statistical analysis gives no indication that Cervarix vaccine may be associated with a risk of CFS.

### **Facial palsy, Guillain-Barre syndrome (GBS), and encephalitis**

Facial palsy, GBS and encephalitis all occur naturally in the population included in the immunisation programme. It is therefore inevitable that some cases will occur in short temporal association with vaccination and that such cases may be reported as suspected ADRs. The MHRA has put in place the 'observed versus expected' analysis specifically to assess such associations.

The observed versus expected analysis indicates that suspected cases of GBS, facial palsy and encephalitis have not been reported after Cervarix vaccination to a greater extent than would be expected, based on background data before the vaccine was introduced. There remains no confirmed evidence that the vaccine is associated with these conditions.

## **CONCLUSIONS**

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

The number and nature of suspected adverse reactions received to date is very much in line with expectations.

The CHM reviewed these data in September 2010 and agreed that following substantial usage, no serious new risks have been identified during use of Cervarix in the UK, and that the balance of benefits and risks remains positive.

During the course of the 2 years, regulatory action has been taken to ensure that the product information adequately reflects the very rare risk of anaphylaxis, warns that people may faint during the injection (as with any injection) and states that swollen glands under the arm may appear for a short time after vaccination.

As with all vaccines, the MHRA and CHM will continue to closely monitor the safety of Cervarix during continued use in the UK.



## 7. REFERENCES

1. Wacholder S et al. Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18: pooled analysis of two randomised controlled trials. *BMJ* 2010; **340**: c712
2. NICE guidelines on diagnosis and management of chronic fatigue syndrome [<http://guidance.nice.org.uk/CG53> last accessed in September 2010]

## 8. GLOSSARY

### **Active treatment**

The drug that is being evaluated in a study

### **Addison's disease**

A disease caused by a partial or total failure in function of the cortex of the adrenal glands (which are located on top of each kidney). The cortex of adrenal glands normally produces substances called hormones which regulate blood pressure, growth and some sexual characteristics

### **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

### **Alopecia**

Hair loss

### **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

### **Aplastic anaemia**

A medical condition where bone marrow does not produce an adequate quantity of red blood cells

### **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

### **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**

**Contusion**

Bruise

**Convulsion**

Intense, involuntary muscular contractions

**Cyanosis**

A bluish discolouration of the skin and mucous membranes, which is due to insufficient oxygen in the blood

**Cytokine**

A small protein released by cells in the immune system that helps the body to generate an immune response to foreign substances

**Diabetes mellitus**

A medical condition in which the body does not produce enough insulin, or when insulin does not work properly. Insulin controls the level of sugar in the blood

**Disproportionality analysis**

Statistical methods used to analyse and understand the association between drugs and adverse events

**Dyspnoea**

Difficulty in breathing

**Eosinophilia**

An increase in the number of white blood cells in the body, usually due to allergies or certain diseases

**Epistaxis**

Bleeding from the nose

**Erythema multiforme**

A type of **allergic reaction** that occurs in response to medications, infections or illness. Its symptoms include inflammatory skin eruptions or rashes. There are two forms: a minor form which is not serious, and a major form (also known as **Stevens-Johnson syndrome**) which is more severe

**Facial palsy**

See **Bell's palsy**

**Fatigue**

Mental or physical tiredness

**Febrile illness**

A non-specific term for an illness accompanied by fever

**Gastrointestinal**

Related to the stomach and intestines

**Guillain-Barre 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

**Lipid**

A group of compounds which include fats and oils

**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

**Meningitis**

An infectious disease characterised by inflammation of the tissues surrounding the brain or spinal cord. Symptoms include fever, headache, vomiting and sensitivity to light

**Metabolism**

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

**Migraine**

A severe headache, usually accompanied by nausea and visual disorders

**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**

**Mydriasis**

Prolonged abnormal dilation (or widening) of the pupil of the eye

**Nasopharyngitis**

Inflammation of the nasal passages and pharynx (the passage leading from behind the nose to the trachea or windpipe)

**Nausea**

Feeling of sickness or an urge to vomit

**Neurogenic bladder**

Bladder dysfunction caused by nerve damage. The main symptom is **urinary incontinence**

**Neutropenia**

An abnormal decrease in the number of particular blood cells called neutrophils

**Oncogenic**

Tending to cause or give rise to tumours

**Oropharyngeal**

Relating to the mouth and pharynx (the passage leading from behind the nose to the trachea or windpipe)

**Palpitations**

Awareness of the heartbeat

**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

**Pancytopenia** A deficiency of blood cells, usually associated with tumours in bone marrow

**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

**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

**Primary care trusts**

NHS groups responsible for local community health services

**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**

**Sensory disturbance**

A term used to describe a group of symptoms such as **parasthesia**, numbness, pain and itching, which are caused by injured nerves in the spinal cord

**Somnolence**

Sleepiness

***Staphylococcus aureus* infection**

A bacterial infection caused by the 'aureas' member of the staphylococcus family. The symptoms are usually abscesses or boils on the skin

**Stevens-Johnson syndrome**

A serious bodywide allergic reaction consisting of a rash on the skin and mucous membranes (also known as **erythema multiforme** major)

**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 available at <http://www.medicines.org.uk/emc/>

**Syncope**

Partial or complete loss of consciousness (a faint)

**Tachycardia**

An abnormal increase in heart rate

**Thoracic**

Related to the chest

**Tinnitus**

Noises in the ear that originate from within the ear or head

**Tonic-clonic**

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

**Transient**

Temporary

**Urinary incontinence**

Inability to control the flow of urine; involuntary urination

**Urinary retention**

Inability to pass urine from the bladder, usually due to an obstruction

**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