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Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK

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ABSTRACT

Introduction: Over 70% of cervical cancers are related to human papillomavirus types 16 and 18. In 2008, the vaccine Cervarix, protecting against these two strains, was introduced into the routine UK immunisation programme for girls aged 12–13 years, with a catch-up in girls aged up to 18 years. As part of the risk management planning for this new campaign, the Medicines and Healthcare products Regulatory Agency (MHRA) anticipated a range of conditions, including chronic fatigue syndrome, which might be reported as adverse events in temporal association with the vaccine.

Methods: Near-real time 'observed vs. expected' analyses were conducted comparing the number of reports of fatigue syndromes submitted via the MHRA's Yellow Card passive surveillance scheme to the expected number, using background rates calculated from the Clinical Practice Research Datalink (CPRD) and estimates of vaccination coverage. Subsequently, an ecological analysis and a self-controlled case series (SCCS), both using CPRD, compared the incidence rate of fatigue syndromes in girls before and after the start of the vaccination campaign and the risk in the year post-vaccination compared to other periods.

Results: The number of spontaneous reports of chronic fatigue following Cervarix vaccination was consistent with estimated background rates even assuming low reporting. Ecological analyses suggested that there had been no change in the incidence of fatigue syndromes in girls aged 12–20 years after the introduction of the vaccination despite high uptake (IRR: 0.94, 95% CI: 0.78–1.14). The SCCS, including 187 girls, also showed no evidence of an increased risk of fatigue syndromes in the year post first vaccination (IRR: 1.07, 95% CI: 0.57–2.00, p = 0.84).

Discussion: The successful implementation of an enhanced pharmacovigilance plan provided immediate reassuring evidence that there was no association between vaccination with Cervarix and an increased risk of chronic fatigue syndromes. This has now also been further demonstrated in more comprehensive epidemiological studies.

1. Introduction

Despite increased screening and improving treatments considerably reducing cervical cancer mortality rates in the UK [1], there are still nearly 1000 deaths per year.

Over 99% of cervical cancers are attributable to human papillomavirus (HPV) infection with over 70% of these related to types 16 and 18 [2,3]. To reduce the burden of disease, the vaccine Cervarix, protecting against these strains, was introduced into the UK national immunisation programme in September 2008. It is offered to all girls aged 12–13 years, with an initial catch-up programme for those aged 14–18 years. The programme is eventually expected to prevent up to 400 deaths per year [4]. The campaign involved immunisation of approximately 2 million girls over the first 2 years, with three doses each over at least 5 months [5,6]. At launch in the UK, Cervarix had not been used routinely in any other country.

The key pharmacovigilance objective in any mass immunisation campaign with a new vaccine is to detect side effects as quickly as possible. However, given the sudden large increase in use it is inevitable that many adverse events entirely coincidental with vaccination will be reported. Unfounded safety concerns can damage confidence in a vaccine so the challenge is to rapidly distinguish potential side effects from coincidental events. To try and address this, the Medicines and Healthcare products Regulatory Agency (MHRA) applied, as enhanced proactive pharmacovigilance alongside routine signal detection activities, statistical methods for near-real time sequential analysis of adverse event reporting via the Yellow Card scheme. This could then be supported by

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epidemiological analyses using the Clinical Practice Research Datalink (CPRD; formerly GPRD).

Based on prior experience, it was known that a range of autoimmune and neuroinflammatory disorders naturally prevalent in the population, were likely to be reported as adverse events following adolescent immunisation. One such condition was chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), characterised by debilitating fatigue and a range of symptoms including malaise, headaches, sleep disturbances, difficulties with concentration, and muscle pain, which has a prevalence of 0.2% in England [7] and 0.006–3% worldwide [8,9]. In 1998, reports of CFS/ME and demyelinating disorders led to suspension of the French adolescent hepatitis B immunisation programme [10]. It took years of epidemiological study to determine that these events were coincidental.

This paper describes the MHRA's proactive pharmacovigilance methodology, applied to reports of chronic fatigue conditions during the first 2 years of the Cervarix immunisation campaign, and subsequent epidemiological analyses.

2. Methods

2.1. Data sources

2.1.1. UK Yellow Card Scheme

Introduced in 1964, the Yellow Card system (www.mhra.gov.uk/yellowcard) is a spontaneous reporting scheme through which health professionals, the public, and pharmaceutical companies can promptly report any suspected adverse drug reaction directly to the MHRA. To date, approximately 670,000 reports have been received. Despite possible under-reporting, an inherent issue with any spontaneous reporting approach, this type of scheme is one of the most established ways of monitoring drug safety in routine clinical practice. The utility of the scheme in vaccine pharmacovigilance was well-demonstrated with the childhood meningitis C vaccine in late-1999 [11].

2.1.2. Clinical Practice Research Datalink

The CPRD holds up-to-date demographic, clinical, prescribing, and referral data extracted from 3.5+ million active electronic medical records throughout the UK (http://www.cprd.com/intro.asp), with historical data on 12.5+ million patients. The data have been extensively used in epidemiological research including several studies on CFS/ME [12–15]. Diagnoses, test results, and referrals are recorded using read codes [16]. The CPRD research group assess the quality and completeness of the extracted data. Patients are considered "acceptable" and GP practices "up-to-standard" if the data from that patient/practice is concluded by the group to be suitable for epidemiological research.

2.1.3. National statistics on immunisation uptake

Regular updates on the estimated number of girls by age who received a dose of Cervarix were obtained via the Department of Health in England and the health departments in Wales, Scotland and Northern Ireland.

2.1.4. 'Observed vs. expected' analysis

Yellow Cards reporting CFS/ME in temporal association with Cervarix (and HPV vaccine where brand was not stated) were followed-up with reporters on an ongoing basis to determine diagnostic certainty. This included reports of post-viral fatigue syndrome (PVFS) and cases describing 'chronic' fatigue. Possible cases, reported in the UK media but not via the Yellow Card Scheme, were also included, with the conservative assumption that diagnosis was confirmed. This analysis was signal generating so the potential for false positives was accepted.

Composite age and gender-specific background incidence rates for CFS/ME and PVFS were estimated using data from the CPRD for the 10 years prior to the start of the campaign. These rates were used along with the weekly uptake data as they became available to estimate the expected cumulative number of diagnoses in vaccinated girls during the first 2 years of the programme.

The maximised sequential probability ratio test (MaxSPRT) was used to generate a 'signal', when the observed number of reports exceeds the expected, by comparing the log-likelihood ratio to a critical value derived from the Poisson distribution [17]. Sequential methods are required to adjust for the multiple testing that occurs with weekly surveillance. Given the likelihood of under-reporting of suspected cases via the Yellow Card Scheme, adjustments were made assuming various hypothetical levels of reporting (10%, 25%, 50%, 75% and 100% of cases reported). This sequential approach has been taken previously for the UK pandemic flu vaccine [18] and in other international vaccine safety studies [19–21].

In each of the first 2 years of the vaccination programme, the observed vs. expected analysis was updated each time a new report of possible chronic fatigue was received or when new uptake data became available. In the first year, due to the higher number of reports expected, analysis was stratified by age but in the second year one analysis covering all ages was conducted.

2.2. Epidemiological analyses

2.2.1. Ecological study

Patients with a clinical diagnosis of a chronic fatigue syndrome, during 2000–2011, were extracted from the CPRD general practice database, in March 2012. Diagnoses were identified via a dated clinical read code according to a pre-defined code list. Given the difficult nature of the diagnosis a range of related terms were considered including CFS/ME, PVFS, fibromyalgia, and neurasthenia [5,6]. An incident diagnosis was defined as the first recorded clinical code per acceptable patient registered in an up-to-standard practice. The incidence of diagnoses per quarter, in girls aged 12–20 years, was calculated overall and by category of first diagnosis. Missing months of birth were randomly assigned. Poisson regression was used to compare trends in incidence rates before (2006–2007) and after (2009–2011) the introduction of the HPV vaccine. Comparative analyses examining the incidence in adults aged 21+ years and boys aged 12–20 years were conducted. A sensitivity analysis, in girls aged 12–20 years, including referrals for fatigue syndromes and symptoms of tiredness, using the predefined list of relevant read codes for referrals and additional codes for symptoms recorded as clinical diagnoses, was also conducted.

2.2.2. Self-controlled case series

Self-controlled case series (SCCS) methodology [22] was used to estimate the risk of diagnosis in the year after first vaccination relative to the risk in the remainder of the patient's time in follow-up during the study period (01/10/2008–31/12/2011). Girls with a record of HPV vaccination and diagnosis of a fatigue syndrome (CFS/ME, PVFS, fibromyalgia, or neurasthenia), occurring during the study period while registered in an up-to-standard practice, were included. Girls with less than 1 year of follow-up were excluded to ensure adequate data. The index date was defined as the date of the first clinical record of a diagnosis of a fatigue syndrome. The 12 month risk window was defined to start the day after the date of first vaccination. Follow-up was censored at the earliest of the practice last data collection date, the date of transfer out of the practice, or 31st December 2011. Age and calendar time, in years, were adjusted for as discrete time-varying covariates.

A sensitivity analysis, including first referrals for, and symptoms of, chronic fatigue syndromes was conducted. The index date in this analysis was therefore the first record of symptoms, referral,

Table 1
Yellow Card and media reported cases of fatigue syndromes.

Year	Age group (years)	Number of spontaneous cases identified			Estimated number of girls receiving at least one dose of Cervarix	Estimated background rate per 100,000 girls per year estimated from the CPRD
		Yellow Card reports	From the UK media only	Retrospectively identified (i.e. not available for real time analysis)		
2008/2009[a]	12–13	8[b]	2	5	320,414	31.2
	17–18	1	0	1	210,808	69.5
2009/2010	12–18	9	0	3	1,005,773	47.4

[a] Note that in 2008/2009 there were no cases reported in 14–16 year olds.
[b] Three were also reported in the UK media.

or diagnosis, whichever was earliest. Further sensitivity analyses first changing the risk window from 12 to 6 and 18 months and secondly including only girls with a specific diagnosis of CFS/ME or PVFS (and not fibromyalgia or neurasthenia) were conducted.

Analyses were conducted using STATA 11.1. Full CPRD read code lists for vaccination and diagnoses (including referrals and symptoms) can be obtained from the authors.

3. Results

3.1. Observed vs. expected analysis

Table 1 describes reports of suspected chronic fatigue syndromes for the first 2 years of the immunisation programme.

Fig. 1 shows the results from the observed vs. expected analysis as it progressed during the same time period. In 2008/2009, for 12–13 year olds, a 'signal' was raised under the assumption that just 10% of events were reported. Only cases reported within the relevant year were included in the real-time analyses. If additional retrospectively identified cases had been available for real-time inclusion the critical threshold would have been briefly surpassed under the assumption that 25% of events were reported (results not shown). Only two cases in older girls were identified for 2008/2009, within expected levels. In 2009/2010, fewer cases were identified, the majority (7/9) in girls aged 16–18 years, and a 'signal' was again only raised assuming 10% reporting.

3.2. Ecological study

1294 incident diagnoses of fatigue syndromes were identified in girls aged 12–20 years in 2000–2011. Fig. 2 shows the rate of diagnoses in girls aged 12–20 years by quarter and that in boys aged 12–20 years and adults aged 21+ years.

From 2003 to 2005 there was a decline in the rate of diagnosis of fatigue syndromes. Comparing the incidence rate for girls aged 12–20 years in 2009–2011 to 2006–2007 resulted in an incident rate ratio IRR = 0.94 (95% confidence interval: 0.78–1.14) suggesting that there was no change in the incidence of fatigue syndromes following introduction of the HPV vaccination. This was also observed in adults (IRR: 0.96, 95% CI: 0.93–1.01). However, the decreasing trend in incidence observed prior to 2006 was seen to continue in boys aged 12–20 years (2009/2011 vs. 2006/2007, IRR: 0.66, 95% CI: 0.50–0.87). This was in part driven by a slight increased incidence in boys in 2006/2007 compared to 2005 while a decrease was observed in girls and adults over the same period. There is no obvious scientific explanation for this beyond natural random variation which, given the lower background rates in boys, is more likely.

Fig. 3 shows the rate of incident diagnoses of fatigue syndromes in girls aged 12–20 years by quarter stratified by type of diagnosis. When comparing the rate of diagnosis for each category for 2006–2007 with 2009–2011, the only significant change is the decreased diagnosis of neurasthenia (IRR 0.08, 95% CI: 0.02–0.24, $p < 0.001$).

The decrease in the incidence of fatigue syndromes, in girls aged 12–20 years, from 2003 to 2005, was also seen when including earlier symptoms and referrals. However, beyond that, a further reduction was seen (2009/2011 vs. 2006/2007 IRR: 0.77, 95% CI: 0.66–0.91, $p < 0.001$) which was not seen when only considering recorded diagnoses.

3.3. Self-controlled case series

187 girls with an incident diagnosis of a fatigue syndrome and a recorded vaccination with the HPV vaccine were identified (01/10/2008–31/12/2011). 98 (52%) had no recorded symptoms or specialist referral prior to diagnosis. 87 (47%) had symptoms of tiredness recorded a median (IQR) 12.5 (3.0–41.7) months before diagnosis. 28 (15%) had a specialist referral 25.6 (5.1–107.4) weeks before diagnosis. A further 15 girls had a first referral 1.3 (0.1–25.1) weeks after their first recorded diagnosis. 53 girls were diagnosed in the 1 year risk window after the first recorded vaccination.

The adjusted conditional Poisson regression model showed no evidence of an increased risk of fatigue syndromes in the year following first vaccination (IRR: 1.07, 95% CI: 0.57–2.00, $p = 0.84$).

The first sensitivity analysis, changing the index date to date of earlier symptoms or referral, also showed no association between vaccination and fatigue syndromes. Given the difficulties associated with diagnosis further sensitivity analyses changing the risk window to 6 and 18 months were considered as well as only including those with a diagnosis of CFS/ME or PVFS. Again, no association of an increased risk was found. Full model results can be seen in Table 2.

4. Discussion

Campaigns with new vaccines require proactive safety evaluation to quickly identify potential risks and prevent unfounded safety concerns. It is inevitable that mass immunisation will lead to serious adverse events being reported whether causally associated with vaccination or coincidental. Having processes in place to evaluate events in near-real time is essential. To meet this challenge for the UK's HPV immunisation programme, the MHRA adopted a strategy of proactive 'enhanced' surveillance via the Yellow Card Scheme supported by epidemiological analyses using CPRD.

A key strength of the Yellow Card Scheme is its coverage, allowing rare adverse events to be rapidly reported by anyone in the UK. As with any passive surveillance, key limitations include variable under-reporting and potentially biased reporting of more severe or acute onset cases. Although passive surveillance alone cannot

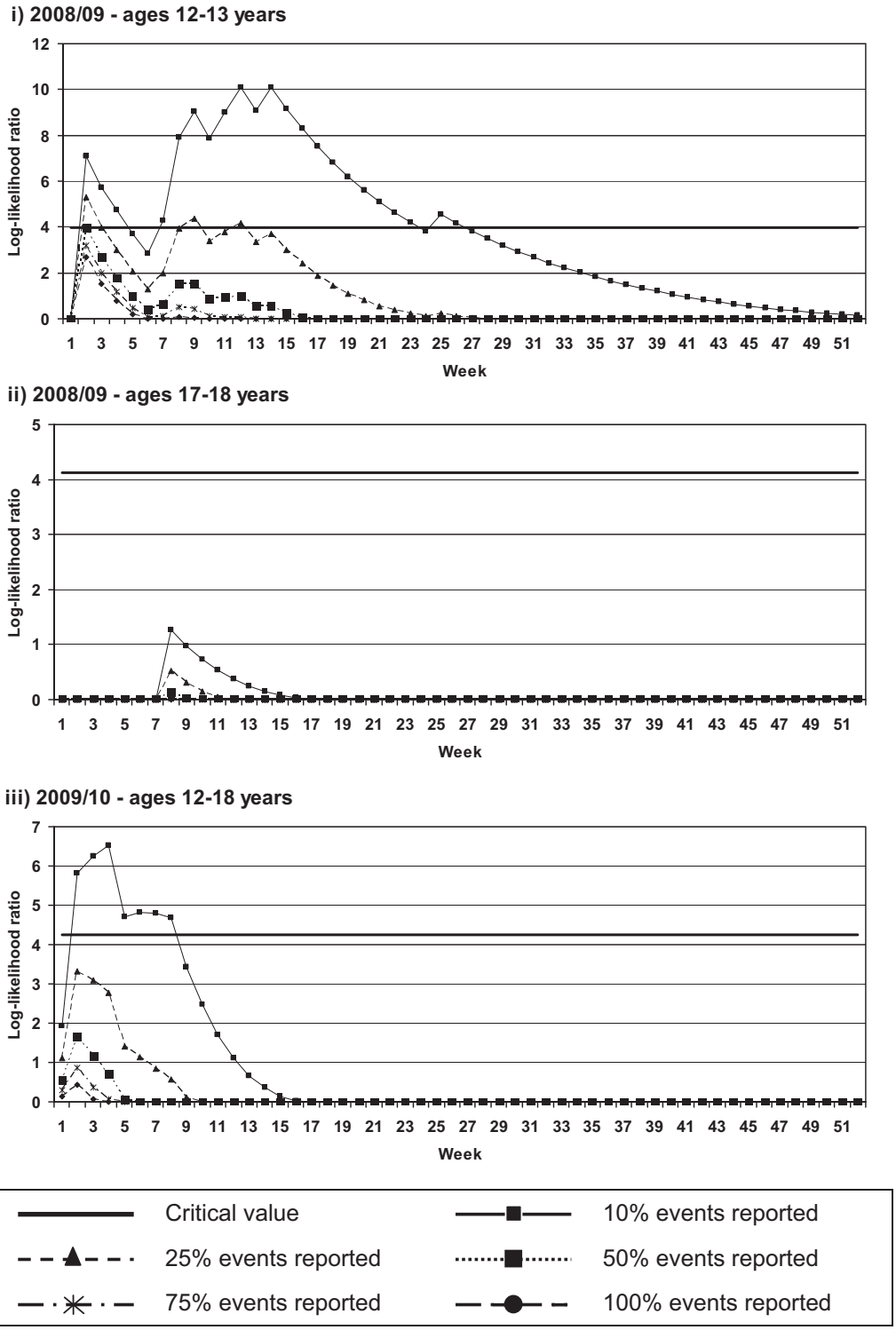

Fig. 1. Real time maximised SPRT for fatigue syndromes for girls in 2008/2009* (i) ages 12–13 and (ii) ages 17–18 and (iii) 2009/2010 ages 12–18.

determine causality, combining it with data on vaccine exposure and background incidence provides a powerful tool for rapid 'signal generation'.

Due to the heterogeneous nature of chronic fatigue syndrome, there are no validated diagnostic tests or specific biological markers for diagnosing it. Diagnosis is based on recognition of the typical symptom pattern after the exclusion of alternative medical and psychiatric conditions [23]. Therefore, a conservative approach was taken to the observed vs. expected analyses, where all spontaneously reported and media cases were included, even those without a definitive diagnosis. In many Yellow Card cases reported as CFS/ME, the available clinical details did not necessarily support such a diagnosis. This may also be true for reports in the media. The threshold for generation of a potential safety 'signal' was reached only if it was assumed that no more than 10% of cases occurring after the vaccine had been reported. Although the level of under-reporting cannot be accurately quantified, it could be assumed that the expected level would be higher than

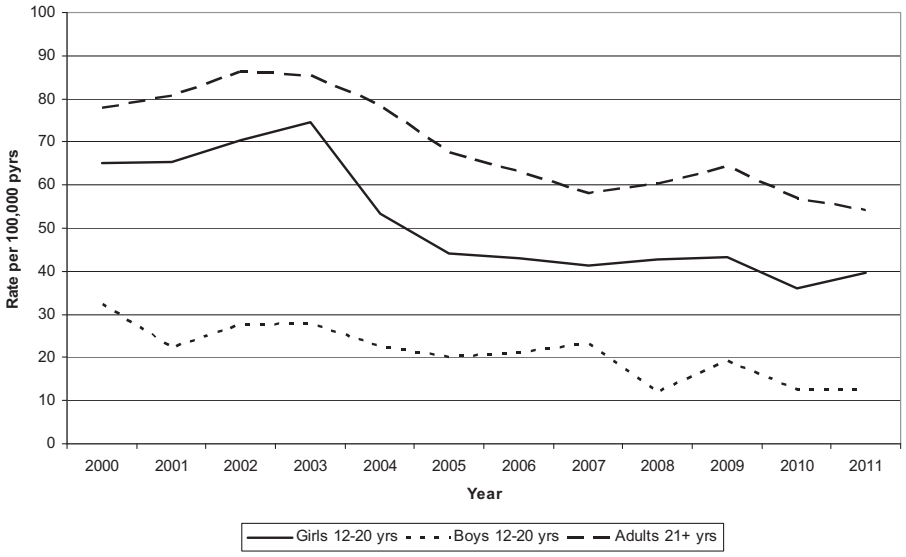

Fig. 2. The incidence of fatigue syndromes in the CPRD 2000–2011.

this as reporting is usually higher during the first phase of a new immunisation programme. Cervarix had 'Black Triangle' status [24] in order to encourage adverse event reporting, and the MHRA issued guidance to encourage reporting at the start of the programme. In addition, the media cases may have stimulated reporting.

There are limitations to the observed vs. expected approach. Given some girls were not vaccinated the appropriateness of using data from the whole CPRD population to estimate age-specific background risks might be questioned as the risk profile of those vaccinated may not be the same as the general population. However, given the high coverage of the vaccine [5], consistently above 85% for one dose, differences are hopefully minimal.

Despite these limitations, it was clear that the observed vs. expected analyses showed no sustained 'signal' of an association of chronic fatigue syndromes with HPV vaccination. No signal was seen in further retrospective observed vs. expected analyses also conducted but not presented here.

Self-controlled case series methods, originally developed to examine the relationship between a time-varying exposure and acute outcomes, have also been used to investigate non-acute outcomes [25]. They can be efficient as they involve only the identification of cases and implicitly control for all fixed confounders.

General practice databases contain data primarily recorded for clinical monitoring rather than research and verifying outcomes is difficult. This is likely to have been an issue here with apparent diagnoses of fatigue syndromes potentially later being ruled out and complicates both the estimation of background rates used for the observed vs. expected analyses and the epidemiological studies. However, there is no reason to believe this has systematically biased the conclusions of the study.

There are two major limitations of the data within the CPRD. Firstly, the recording of HPV vaccination within the CPRD is low. The vaccine is primarily administered in school and, although reporting of the immunisation to the GP is encouraged, only approximately 40% of girls had a record for a vaccination whereas we know, from the national uptake data, that coverage has been much higher. This made the use of the SCCS methodology particularly pertinent, as there is no need to include non-exposed patients, but also means that there is an increased chance of selection bias should symptoms

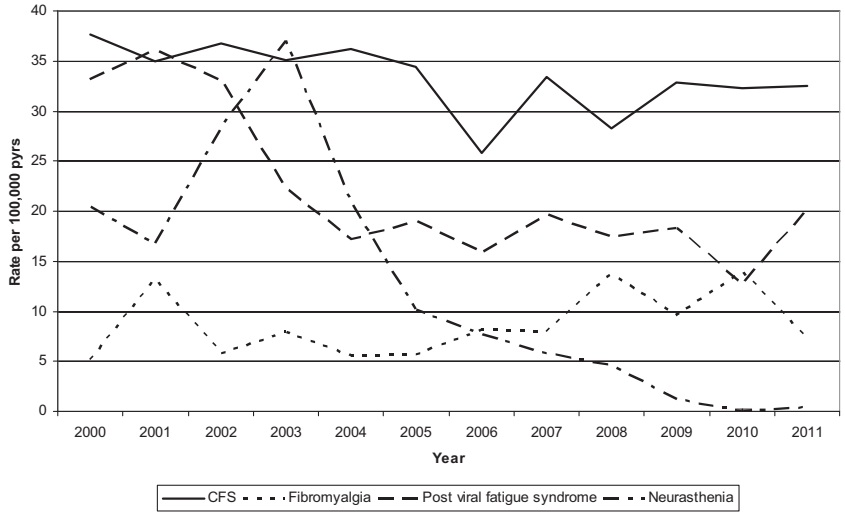

Fig. 3. The incidence of fatigue syndromes in girls aged 12–20 years by type of diagnosis 2000–2011.

Table 2
Self-controlled case series analyses results.

Analysis	Details of SCCS statistical analysis[a]	Number of identified cases in vaccinated girls	IRR	95% CI	*p*-Value
Primary analysis	Index date – first diagnosis of fatigue (including CFS/ME, PVFS, fibromyalgia, and neurasthenia) Risk window – 12 months	187	1.07	0.57–2.00	0.84
Sensitivity analyses	Index date – first symptoms/referral/diagnosis of fatigue (including CFS/ME, PVFS, fibromyalgia, and neurasthenia) Risk window – 12 months	193[b]	0.99	0.54–1.82	0.97
	Index date–first diagnosis of fatigue (including CFS/ME, PVFS, fibromyalgia, and neurasthenia) Risk window – reduced to 6 months	187	1.24	0.67–2.29	0.50
	Index date – first diagnosis of fatigue (including CFS/ME, PVFS, fibromyalgia, and neurasthenia) Risk window – extended to 18 months	187	1.47	0.77–2.82	0.25
	Index date – first diagnosis of CFS/ME or PVFS only (excluding fibromyalgia and neurasthenia) Risk window – 12 months	161	1.03	0.51–2.07	0.93

[a] Details include: (1) The index date for the analysis – i.e. the date for which the fatigue syndrome is defined to have started. (2) The risk window following the first recorded HPV vaccine exposure.
[b] Includes 6 cases with symptoms of tiredness or a referral to specialist care for fatigue with no recorded clinical diagnosis.

or diagnosis of a fatigue syndrome have stimulated retrospective recording of the vaccination. It additionally meant that it was not possible to define a separate risk period following each of the three doses without further reducing the number of patients available for study. This issue with recording raises the potential for misclassification of vaccination status when the first recorded vaccination date is not actually of the first dose but of a subsequent injection. However, over 92% of first recorded vaccinations are specifically coded as the 'first HPV vaccination' so impact of any misclassification is likely to be minimal. Secondly, CPRD data is collected primarily for clinical monitoring so diagnoses have not been verified. Given the difficult nature of the diagnosis this is a concern so a broad definition was used initially with a subsequent sensitivity analysis restricting the read codes used to identify cases. Neither of these analyses found any association between the vaccine and fatigue syndromes.

One additional assumption made in the SCCS is that the likelihood of exposure is not changed by experiencing the outcome. However, there is no reason to suspect that girls with fatigue syndrome would be less likely to receive the vaccination and, indeed, repeating the models excluding pre-exposure time also shows no association (results not shown).

In summary, this study shows no evidence of an increased risk of chronic fatigue syndromes with Cervarix. While there are established limitations to epidemiological methods we can be reassured by the consistent findings. This proactive strategy for signal detection has led to a large evidence base regarding its safety. In particular, this meant that when initial concerns were raised about the risk of fatigue syndromes, real-time pharmacovigilance was able to provide reassurance that there was no evidence of an association.

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