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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 (1.07, 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

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by 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,

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