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COMMENTARY

Safety Concerns with HPV Vaccines Continue to Linger: Are Current Vaccine Pharmacovigilance Practices Sufficient?

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1 Introduction

The current paradigm of vaccine pharmacovigilance includes three stages: signal detection, development of a causality hypothesis, and testing of the causality hypothesis [1]. Signal detection in the postmarketing setting largely relies on spontaneous reports of adverse events (AEs) following immunization (AEFI) and literature case reports. The development of a causality hypothesis involves an assessment of the relevant case series using standardized case definitions [2], individual-level causality criteria [3], and 'observed versus expected' calculations [4]. Testing of the causality hypothesis follows, using large epidemiology studies that rely on diagnostic coding or insurance claims data for measuring outcomes of interest. Such studies allow regulatory and public health agencies to make an estimation of risk at the population level from which conclusions on causality are drawn.

Over the last several years, there has been focus on a number of safety signals for the human papillomavirus (HPV) vaccines, including complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), and chronic fatigue syndrome (CFS). These signals have been a challenge for public health authorities because routine vaccine pharmacovigilance practice is not sufficient to understand suspected harms that are poorly defined and whose pathophysiology are not completely understood. Furthermore, estimations of risk at the population level fail to acknowledge that vaccines may cause harm in subgroups with individual-level risk factors for AEFI.

Novel approaches to vaccine pharmacovigilance are required to more fully understand this safety concern for HPV vaccines. In this issue of *Drug Safety*, Ozawa et al. describe a case series of girls from Japan who experienced multiple symptoms suspected to be caused by the HPV vaccine. They report on diagnostic findings underlying these symptoms and they take a unique approach to the analysis of temporality in their causality assessment [5].

2 The Case of the Human Papillomavirus (HPV) Vaccine

Since 2013, there have been multiple reports from different countries describing case series of suspected harms of a similar nature after HPV vaccination. The first report was a case series of six girls with POTS from the US [6]. Following soon after were case series descriptions of CRPS from Japan [7], long-lasting fatigue from The Netherlands [8], and orthostatic intolerance and POTS from Denmark [9]. Similar reports from Italy [10], Mexico [11], and Colombia [12] have subsequently been described. Each of the reports details multiple symptoms experienced by patients, including headache, fatigue, dizziness, pain, cognitive dysfunction, and sleep disturbances. Often also reported are abdominal complaints and skin rashes, as well as sensory disturbances and motor weakness in the extremities. Although a variety of diagnostic labels are

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suggested by the different authors, a feature of dysfunction of the autonomic nervous system is consistent between all the reported case series.

3 A New Report from Japan

Ozawa et al. have described their assessment of another series of girls who presented to their speciality clinic with multiple symptoms suspected to be caused by HPV vaccination [5]. They evaluated 163 patients using diagnostic criteria for vaccine-related AEs following HPV vaccination that had been previously developed in Japan. These criteria include both subjective and objective findings, as well as both inclusion criteria and exclusion criteria. 'Definite' cases required both subjective and objective findings, while 'probable' cases required only subjective findings. Seventy-two of the 163 patients met sufficient criteria to be considered as vaccine-related ('definite' or 'probable'). Major symptoms included prolonged fatigue, chronic headache, widespread pain, limb shaking, dysautonomia symptoms, motor and sensory impairment, sleep disturbances, and cognitive impairment. The most frequent objective findings seen in these 72 patients were orthostatic intolerance (70.8%), flattened digital plethysmography (70.2%), and focal abnormality of cerebral blood flow in single-photon emission computed tomography (75%). The authors label the symptoms experienced after HPV vaccination as 'CRPS and autonomic and cognitive dysfunction'.

4 Traditional Vaccine Pharmacovigilance, the Route of Public Health Authorities

In their response to this safety concern for HPV vaccines, public health authorities have kept to the traditional vaccine pharmacovigilance paradigm; however, there is evidence of a lack of consensus on movement through the various stages. In Europe, the European Medicines Agency (EMA) conducted a safety referral in 2015 and concluded that the available evidence was insufficient to support a causal hypothesis; thus, there was no recommendation for further investigation of either CRPS or POTS with epidemiological studies [13]. The National Institute for Health and Welfare in Finland has initiated an approach to understand the signal within their own country. In an effort to establish a denominator for observed versus expected analyses, they have published data on the baseline incidence of POTS and CFS prior to introduction of the HPV vaccine into their childhood vaccination program [14]. Two countries, the UK and Norway, have performed epidemiological studies to investigate a causal hypothesis between HPV vaccination and CFS, neither of which found an increased incidence of CFS after the initiation of HPV vaccination programs in their countries [15, 16]. The US FDA has included CRPS as an endpoint in a planned Sentinel/PRISM study for Gardasil 9 [17], and a recent review of POTS/HPV vaccination by authors from the Mayo Clinic suggested that a population-based study would be required to compare the incidence of POTS in adolescents who have and have not received the HPV vaccine [18].

5 Where Are We Now? Has Traditional Vaccine Pharmacovigilance Been Sufficient?

Currently, we have a signal based on both spontaneous reports and published case series that is best characterized as a potential association between HPV vaccination and dysfunction of the autonomic nervous system. However, movement through the stages of the traditional vaccine pharmacovigilance paradigm has stalled; the development and subsequent testing of a causality hypothesis has been complicated by the lack of a case definition for the multiple symptoms that constitute this signal. Consequently, it is difficult to identify the appropriate case series for clinical review, to apply diagnostic case criteria, and to design follow-up epidemiological studies. Furthermore, causality assessment is hindered by a lack of understanding of the underlying pathophysiological process of the AEFI.

The challenges with application of the current vaccine pharmacovigilance framework to investigate this signal, combined with the failure of public health authorities to communicate these limitations, has been largely unsatisfactory to the public. National patient advocacy groups are working across country boundaries using social media to communicate with others about their experiences, describing symptoms after the vaccine, expressing frustration due to a lack of recognition from the medical system, and sharing their experiences with alternative treatments. Confidence in the HPV vaccination may be declining in some countries, as evidenced by decreased uptake of the vaccine in recent years [19, 20].

6 How Can We Move Forward?

Novel approaches to vaccine pharmacovigilance are required to more fully address this important safety concern for HPV vaccines. An additional requirement is incorporation of the progress in vaccine safety science which acknowledges that AEFI may be individually determined. Continued collection and assessment of all kinds of evidence, including searching for subgroups at risk, can lead to better estimations of the probability of causality.

At the Uppsala Monitoring Centre, we performed and published a novel approach to case series identification for

thorough signal evaluation [21]. A data-driven exploratory cluster analysis of HPV vaccine reports contained within VigiBase® was used to identify natural groupings in HPV vaccine reports based on AE-term profiles. Our analysis revealed a large number of reports with a pattern of AEs, including headache, dizziness, fatigue and syncope, distinguished from more common AEs by their serious nature. Included in this group were reports that contained the diagnostic labels of POTS, CFS, and CRPS, but the majority of the reports lacked explicit diagnoses. Previous evaluations of this safety concern that focused separately on individual diagnoses likely excluded many clinically relevant cases.

Ozawa and colleagues have also contributed a new approach to one criteria in causality assessment—temporal association [5]. Typically, an analysis of temporal association is made at the individual level, looking for a consistent time to onset of symptoms after vaccination. However, a large variation of individual incubation times has consistently been noted in the various case series of this signal. An argument against causality using this variation in individual temporality may be appropriate for well-understood clinical outcomes; however, such arguments may not be appropriate for clinical pathologies whose biological mechanisms and/or phenotypic expression may be more complex. In this Japanese cohort, the period from administration of the first dose of vaccine to symptoms ranged from 1 to 1532 days. A slight majority of the girls experienced their symptoms after the third dose of the vaccine (52.8 %), while only 16.7% experienced symptoms after their first dose. However, an analysis of temporality on the population level demonstrated that peak periods of HPV vaccination, and of the onset of this post-vaccination symptom complex, overlapped in Japan.

There is an emerging field within vaccinology called adversomics, which acknowledges the fact that AEFI may be individually determined as there is interindividual variation in vaccine responses based on differences in innate immunity, microbiomes, and immunogenetics [22]. Indeed, the European experience with the pandemic H1N1 vaccine Pandemrix and narcolepsy suggests an interplay between genetics and environmental triggers [23]. There is preliminary evidence to suggest that there may be a subgroup of individuals at risk for this AEFI following HPV vaccination. An epidemiological study conducted in Denmark by Mølbak et al. found that vaccinated subjects with severe adverse reactions had more interaction with medical services prior to vaccination compared with vaccinated subjects without reactions [24]. Furthermore, autoantibodies to G protein-coupled receptors in the nervous system, such as β2-adrenergic and muscarinic-2 receptors have been isolated from two subjects in the US [25, 26] and in a large proportion of a sample of patients in Denmark (Mehlsen J, unpublished data). A recent systematic review details the evidence to support a role of such autoantibodies in syndromes of orthostatic intolerance, including POTS [27]. Autoantibodies to these receptors have also been previously linked with CRPS [28] and CFS [29]. This pathophysiology could explain the pattern of symptomatology that has been consistently described in the multiple case series reported, as well as the variety of diagnostic labels used by reporting physicians. Taken together, these findings may indicate that vaccination has served as a trigger for manifestation of an underlying autoimmune disorder in genetically predisposed individuals. Continued research may lead to identification of subgroups at risk of autonomic dysfunction whose considerations for HPV vaccination might be different from those who are not.

Traditional vaccine pharmacovigilance must evolve to support continued research for the purpose of improved assessments of causality that aligns with the progress in vaccine safety science.

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Compliance with Ethical Standards

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