Adverse events after quadrivalent human papillomavirus vaccination

A population cohort study in Denmark and Sweden finds no consistent evidence for causal associations between the quadrivalent human papillomavirus vaccine and a wide range of venous, autoimmune and neurological adverse outcomes.

Overview: Human papillomavirus (HPV) infects squamous epithelia, such as the skin and the mucosae of the upper respiratory and anogenital tracts. About 40 types of HPV can infect the genital tract. Although most infections are asymptomatic and self-limiting, genital infection by HPV is associated with anogenital cancers and genital warts in both men and women, and cervical cancer in women. HPVs are classified as either high-risk or low-risk types depending on their association with the development of cancer (The Green Book 2013). Genital warts were diagnosed in 73,418 people in the UK in 2013 (Health Protection Report 2014).

Cervical cancer is the 2nd most common cancer in women worldwide and is the 11th most common cancer in women in the UK. More than 70% of cervical cancers are attributed to two types of HPV: HPV 16 and HPV 18 (Health Protection Agency, now part of Public Health England). The September 2013 issue of Eyes on Evidence covered research by Ali et al. (2013) that suggested a reduced incidence of genital warts after the introduction of vaccination against HPV for girls and young women in Australia.

See the NICE Evidence Services topic page on immunisation in children for a general overview of this area.

Current advice: In the UK, a vaccine against 4 types of HPV (quadrivalent vaccine) has been routinely offered to girls aged 12–13 years since September 2012, with ‘catch-up’ programmes available for older girls (mainly aged 13–18 years).

NICE has guidance on reducing differences in the uptake of immunisations. The ‘Green book’ from Public Health England provides information about vaccines and vaccination procedures used in the UK, including the vaccine for HPV.

New evidence: Arnheim-Dahlström et al. (2013) reported a cohort study of serious adverse events in all girls aged 10–17 years in Denmark and Sweden (n=997,585) and a subgroup of those who received at least 1 of 3 doses of the quadrivalent HPV vaccine (n=296,826). Data on vaccinations were obtained from national registers and could be linked with other national databases via unique personal identification numbers. Adverse event data for 53 outcomes were obtained from national patient registers in both countries using codes from the International Classification of Diseases 10th revision.

Adolescent girls were followed from the age of 10 years (or October 2006, whichever came latest) until the age of 18 years or end of follow-up (December 2010). Follow-up also ceased if the girl had an adverse event, received a bivalent HPV vaccine, emigrated or died.
Each possible adverse event was assessed separately, and each analysis excluded any girls who had the outcome event before entry to the study cohort. Analyses were adjusted for country, age, year, and parental education level, country of birth, and socioeconomic status. Autoimmune and neurological outcomes were considered potentially relevant if they occurred up to 180 days after vaccination (for each of the 3 doses). Venous thromboembolic events were considered potentially relevant for up to 90 days after vaccination.

Overall, 696,420 doses of vaccine were administered; of girls who received the first dose, 80% received the second dose and 54% received all 3 doses. Of 53 outcomes analysed, 29 occurred at least 5 times and were analysed further. Neurological adverse events and venous thromboembolism were not significantly higher among girls who received the vaccine. For autoimmune outcomes, girls who received the vaccine had a significantly higher rate of Behcet’s syndrome (rate ratio=3.37, 95% confidence interval [CI] 1.05 to 10.80), Raynaud’s disease (rate ratio=1.67, 95% CI 1.14 to 2.44) and type 1 diabetes (rate ratio=1.29, 95% CI 1.03 to 1.62). However, after confirmatory analyses the authors concluded that there was no consistent evidence for a causal association between vaccination and these autoimmune disorders.

Limitations of this study included that the date of onset for symptoms of adverse events was not known. As such, diagnosis could have occurred after vaccination for symptoms that started before vaccination, artificially increasing the number of recorded cases. Furthermore, the contact with health professionals at vaccination provided an opportunity to assess symptoms that would not otherwise have been reported, and subsequent diagnosis could be incorrectly attributed to vaccination. Conversely, symptoms starting in the potentially relevant period after vaccination may not have been diagnosed until after the period of interest expired, and may not have been captured.

Commentary: “HPV vaccines contain virus-like particles that mimic viral proteins but have no genetic material, so are incapable of replicating. There is, therefore, no biologically predictable mechanism whereby they may cause adverse events, unlike live vaccines, such as measles, which do replicate and may on occasion cause an attenuated form of the disease associated with the wild virus. However, as with any vaccine, it is important not to dismiss the possibility of serious adverse effects arising from an unknown and unexpected biological mechanism. This recently happened with an H1N1 pandemic strain influenza vaccine, which was shown, albeit rarely, to cause narcolepsy (Miller et al. 2013).

“The UK already has extensive post-licensure experience with the unadjuvanted quadrivalent HPV vaccine, which replaced the bivalent oil-in-water adjuvanted vaccine in the national HPV immunisation programme in 2012. Over 120 million doses of quadrivalent HPV vaccine have been given worldwide, and a large observational cohort study similar to that reported by Arnheim-Dalstrom et al. (2013) has been conducted using the US Vaccine Safety Datalink (Gee et al. 2011), with no safety signals of concern raised.

“This additional safety data from Denmark and Sweden is, therefore, essentially confirmatory and will not have any immediate impact on current guidance or practice. However, given the potential for concerns about vaccine safety to arise without warning, this study adds further weight to the already substantial body of evidence supporting the safety of this highly efficacious vaccine.” – Professor Elizabeth Miller, Consultant Epidemiologist, Immunisation, Hepatitis and Blood Safety Department, Public Health England

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