Quadrivalent and nonavalent HPV vaccine: Ovarian safety research

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Abstract

Human papillomavirus (HPV) vaccination may prevent up to 90% of oncogenic HPV infection. Quadrivalent and 9-valent vaccines and HPV testing are replacing the Papanicolaou cervical screening programme to reduce cervical cancer in Australia, which is now mostly confined to women not accessing regular screening. HPV vaccine marketing, licensing and advisory body statements of ovarian safety have followed case series of premature ovarian insufficiency (POI) in vaccine recipients. What evidence supports these statements? Adolescent ovarian safety research post quadrivalent and nonavalent vaccines were reviewed up to 2018. Controlled adolescent safety studies, studies reporting on menstrual function and studies addressing fertility concerns were analysed for design, internal validity, generalizability and outcome. No research has established ovarian safety post HPV vaccination. Two observational studies report 48% and 45% of young women experience irregular menses post vaccine. Research claiming to evidence reproductive safety in response to public concern about fertility effects of HPV vaccination was invalidated by correction for irregular menses, the most frequent presenting sign in POI. Existing vaccine ovarian safety statements are unevidenced. Possible autoimmune and toxicological vaccine effects have been postulated. Currently available post-marketing experience indicates a pressing need to investigate ovarian health after HPV vaccination. In the context of currently advocated long-acting reversible and other hormonal contraception, detection of an ovarian safety problem will be delayed until seeking pregnancy. HPV vaccine ovarian safety statements may confound vaccine adverse event reporting efficiency, reduce vaccine safety datalink effectiveness, delay ovarian safety research and contribute to reduced public vaccine confidence. Uptake of human papillomavirus (HPV) vaccine remains low in many countries, although the bivalent and quadrivalent HPV vaccines given as a three-dose schedule are effective in the prevention of precancerous lesions of the cervix in women. Simpler immunisation schedules, such as those with fewer doses, might reduce barriers to vaccination, as may programmes that include males. Uptake of human papillomavirus (HPV) vaccine remains low in many countries, although the bivalent and quadrivalent HPV vaccines given as a three-dose schedule are effective in the prevention of precancerous lesions of the cervix in women. Simpler immunisation schedules, such as those with fewer doses, might reduce barriers to vaccination, as may programmes that include males. Australia has a comprehensive, fully funded, national human papillomavirus (HPV) vaccination program with high coverage. A three-dose course of quadrivalent HPV vaccine (4vHPV) was introduced through the National Immunization Program (NIP) as a school-based program for 12 to 13-year-old females in 2007 and males in 2013, with catch-up programs for other age groups HPV vaccination primarily aims to protect against cervical, anogenital and oropharyngeal cancers, and high-grade cervical lesions related to HPV infection Australia has been a world leader in demonstrating early program impacts, including declines in HPV prevalence, high grade cervical lesions and genital warts, as well as herd immunity effects, such as a decline in genital wart incidence in heterosexual males prior to the inclusion of males under the NIP [3]. Globally, HPV vaccine programs have been uniquely affected by concerns and issues related to vaccine safety that have negatively impacted upon vaccine uptake Although questions around safety have arisen in Australia, particularly in the early years of the program, relatively high uptake has been sustained with 80.2% three dose coverage among females and 75.9% among males in 2017, measured at 15 years of age .HPV vaccine safety has been evaluated in pre-licensure clinical trials, post-marketing surveillance systems and observational studies worldwide While possible signals for an association of HPV vaccine with Guillain-Barré syndrome (GBS)and venous thromboembolism (VTE) were previously identified, these were excluded in subsequent observational studies Associations of HPV vaccine with other specific conditions and syndromes, including postural orthostatic tachycardia syndrome (POTS), chronic fatigue syndrome (which overlaps with POTS), complex regional pain syndrome (CRPS) and primary ovarian insufficiency (POI) have been the subject of case reports and media interest While observational studies and expert reviews have not supported causal associations these continue to be proposed. Only syncope has been consistently associated with HPV vaccination and is known to be associated with vaccination more generally While generally benign and categorized as an immunization anxiety-related reaction (rather than related to vaccine constituents), syncope following

vaccination carries the risk of harm from syncope-related injury.The initial safety concerns which arose following the introduction of the HPV vaccination program for females in Australia included a potential signal for anaphylaxis and a series of reports of demyelinating syndromes In Australia, spontaneous reports of adverse events (AE) following vaccination are made to the national regulator of vaccines and other therapeutic goods, the Therapeutic Goods Administration (TGA). A Gardasil Expert Panel, established by the TGA, found that the incidence of demyelinating disorders following HPV vaccination was no higher than expected by chance, and that the rate of anaphylaxis was similar to that for other vaccines A high rate of syncope was reported as an early concern but later found to be consistent with expected rates .Following these evaluations, and as one of the first countries to implement a fully funded male program, a period of enhanced surveillance was implemented prospectively under the vaccine safety plan for introduction of the male program. Specifically, school-based AE surveillance was strengthened during 2013 and 2014 by: a) ensuring school immunization nurses recorded data on all AE occurring at the time of, or shortly after, vaccination (typically notified in the first four hours while immunization teams were still onsite at schools); b) a focus on collecting data on four pre-specified significant acute AEs: 1) anaphylaxis; 2) loss of consciousness (including syncope); 3) generalized allergic reaction and; 4) any condition requiring emergency department presentation or hospitalization [33]. During this period there was also more frequent analysis and reporting of data, intended to closely monitor safety in the new cohort (males) and compare it with females Safety surveillance data is now available for a large cohort of Australian adolescents over 11 years, including five years of data for males. Over this period, 4vHPV accounted for 99.9% of doses. We analyzed AE following 4vHPV doses administered between April 2007 and December 2017, focusing on determining age and sex-specific reporting rates, analyzing the impact of enhanced surveillance, and examining adverse events of special interest (AESI).

Biography :

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