Drug Saf (2013) 36:393–412
DOI 10.1007/s40264-013-0039-5

REVIEW ARTICLE

Safety of Human Papillomavirus Vaccines: A Review

Kristine K. Macartney · Clayton Chiu · Melina Georgousakis · Julia M. L. Brotherton

Published online: 1 May 2013

Abstract Vaccination to prevent human papillomavirus (HPV)-related infection leading to cancer, particularly cervical cancer, is a major public health breakthrough. There are currently two licensed HPV vaccines, both of which contain recombinant virus-like particles of HPV types 16 and 18 (which account for approximately 70 % of cervical cancer). One vaccine also protects against HPV types 6 and 11, which cause genital warts. The safety profile of both vaccines was assessed extensively in randomised controlled clinical trials conducted prior to licensure and has been further elucidated following licensure from surveillance and specific studies in large populations. This review aims to examine current evidence regarding the safety of HPV vaccines. In summary, both vaccines are associated with relatively high rates of injection site reactions, particularly pain, but this is usually of short duration and resolves spontaneously. Systemic reactions have generally been mild and self-limited. Post vaccination syncope has occurred, but can be avoided with appropriate care. Serious vaccine-attributable adverse events, such as anaphylaxis, are rare, and although not recommended for use in pregnancy, abnormal pregnancy outcomes following inadvertent administration do not appear to be associated with vaccination. HPV vaccines are used in a three-dose schedule predominantly in adolescent females: as such case reports linking vaccination with a range of new onset chronic conditions, including autoimmune diseases, have been made. However, well-conducted population-based studies show no association between HPV vaccine and a range of such conditions. Whilst this reassuring safety profile affirms the positive risk benefit of vaccination, as HPV vaccine use expands into more diverse populations, including males, ongoing safety assessment using well-conducted studies is appropriate.

K. K. Macartney (✉) · C. Chiu · M. Georgousakis
National Centre for Immunisation Research and Surveillance (NCIRS), Kids Research Institute, The Children's Hospital at Westmead, Cnr Hawkesbury Road and Hainsworth Street, Westmead Locked Bag 4001, Westmead, NSW 2145, Australia
e-mail: kristine.macartney@health.nsw.gov.au

K. K. Macartney
Department of Microbiology and Infectious Diseases, The Children's Hospital at Westmead, Westmead, Australia

K. K. Macartney · C. Chiu
Discipline of Paediatrics and Child Health, University of Sydney, Sydney, Australia

J. M. L. Brotherton
Victorian Cytology Service, Carlton, Australia

1 Introduction

HPV infection is a necessary step in the pathogenesis of cervical, other anogenital and some non-genital cancers [1, 2]. Primary prevention of infection with oncogenic HPV types has the potential to prevent morbidity and mortality worldwide. Cervical cancer alone is the fourth most common cause of cancer-related death worldwide [3, 4]. In addition to causing cancer, HPV infection also causes genital warts, the most common sexually transmitted disease in many developed country settings [5–7].

Two HPV vaccines are available: the bivalent vaccine Cervarix® (2vHPV, GlaxoSmithKline Biologicals, Belgium), which protects against the two oncogenic HPV types 16 and 18 that account for ~70 % of cervical cancer, and the quadrivalent vaccine Gardasil® (4vHPV, Merck and Co., USA), which protects against 16 and 18, as well as the non-oncogenic types 6 and 11, predominantly

responsible for genital warts and other non-malignant lesions. HPV antigens in both vaccines are composed of L1 proteins specific to each HPV type, which are derived using recombinant technology (yeast or insect cell in vitro expression systems) and form conformationally intact non-infectious virus like proteins (VLPs). The vaccines also contain adjuvants, which assist in enhancing the humoral immune response. For 4vHPV the adjuvant is a proprietary aluminium hydroxyphosphate sulphate system and for 2vHPV the adjuvant system is called AS04 and contains both an aluminium salt and monophosphoryl lipid A. [8, 9].

The clinical efficacy of these vaccines in the prevention of persistent HPV infection and intraepithelial neoplasia (potentially pre-cancerous lesions) at the cervix in women has been demonstrated in pre- and post-licensure studies [10–12]. Following impressive clinical trial results in females, both vaccines were made available for use from 2006–2007, with the 4vHPV vaccine now registered in 127 countries and an estimated >95 million doses distributed worldwide (Dr Carlos Sattler, personal communication, Merck, July 2012) and 2vHPV registered in >115 countries with >33 million doses distributed (Kristin Verschueren, personal communication, GSK, July 2012). Recently, population-based vaccination of males using 4vHPV has also been recommended in countries such as the USA, Canada and Australia [13–16] based on efficacy of this vaccine against vaccine-type persistent infection and intraepithelial neoplasia in anogenital sites in males [17]. The widespread availability of these vaccines with expanding use into new settings, particularly less developed countries, underpins the importance of reviewing the body of evidence for safety. Although there is no a priori reason to expect that the safety of HPV vaccines would be particularly different to other inactivated vaccines[18], concerns regarding perceived HPV vaccine safety issues have at times received extensive media attention and have the potential to reduce vaccine uptake [19, 20]. This review aimed to assess all available published safety data on both HPV vaccines, including randomised clinical trials, meta-analyses and data from post-licensure studies.

2 Methods

Articles cited in this review were obtained by searching OVID Medline (1946–May 2012) and OVID EMBASE (1980–May 2012) databases up to May 2012. Individual searches were completed on HPV vaccine safety, HPV vaccine trials and post-licensure studies, and HPV vaccines and pregnancy. Both database controlled vocabulary terms and commonly used free-text terms for HPV vaccines and/or safety were used: a full list of all search terms is available on request. There was no language restriction; however, only articles with English language (abstract or more) were reviewed. The bibliographies of identified articles and reviews were hand-searched to identify additional studies. Internet search engines were also queried for 'HPV vaccine case reports'. Formal inclusion and exclusion criteria were not applied for the purposes of selecting studies for the review; however, the authors endeavored to cite all studies (or pooled analyses) that contained original data, irrespective of the study type (e.g. controlled trial, case report, etc). Position statements and immunisation guidelines were also reviewed.

3 Pre-Licensure Controlled Clinical Trials and Long-Term Follow-Up Studies

The pre-licensure studies examining the safety of both 4vHPV and 2vHPV vaccines were extensive. In addition, a number of controlled clinical studies have continued past their pre-specified completion dates, with long-term follow-up of safety as well as immunogenicity/efficacy outcomes. Additional randomised controlled studies have been conducted in new populations in Korea, China, Japan and Vietnam [21–25]. Safety endpoints in most studies included local and systemic adverse events (AEs), serious AEs (SAEs), death and new onset medical conditions, including chronic and/or autoimmune disease. Pregnancy outcomes were also assessed and are discussed separately below. Many results presented below are from pooled analyses, which give the advantage of including large numbers of participants. Despite ongoing efforts to harmonise the categorisation and reporting of vaccine safety outcome measures in clinical trials [26], limitations on combining results from studies with different designs and/or outcome measures exist. Nevertheless, the results for most studies within these analyses were generally consistent.

3.1 Summary for 4vHPV from Clinical Trials

A pooled analysis on several early and pivotal trials [27–31] involving a total of >20,000 females aged 9–26 years and about 1,350 males aged 9–16 years, mostly from Europe, North and Latin America, showed that injection site reactions (ISR) were significantly more common in vaccine recipients compared with recipients of aluminium-containing placebo or non- aluminium placebo injections [32]. Injection site pain was most common (83 vs. 77 vs. 49 %, respectively, for the 3 recipient groups) with severe pain reported in 4 % of recipients compared with 2 % receiving aluminium-containing placebo. Erythema (24 versus 18 or 13 %) and swelling (24 versus 16 or 8 %) were also more common in vaccine recipients. Common systemic adverse experiences did not differ markedly

between groups, with headache most common (26 %), followed by fever (13 %) and nausea (6 %) [32].

In this analysis there was no significant difference in the frequency of SAEs overall or by system organ class (9 groups) over a median follow-up period of 3.6 years and >34,000 person-years-at-risk [32]. The five reported vaccine-related SAEs were not of any particular cluster [32]. Deaths occurred in 0.1 % of both vaccine and control recipients, respectively, with no death deemed related to the vaccine study [32]. The overall proportion reporting new onset autoimmune conditions was not different between both groups (2.4 % in each); specific conditions that were nominally higher among 4vHPV vaccine recipients included thyroiditis, rheumatoid arthritis and proteinuria, although each occurred in <0.1 % [32]. However, given the relative rarity of these individual conditions, even analysis of pooled data from many clinical trials does not provide enough participants to detect meaningful differences in such low-incidence events (discussed further in Sect. 5).

Another pooled analysis of trials in approximately 6,000 Latin American females aged 9–24 years also found more ISR in vaccine compared with placebo recipients (85 versus 73 %). Proportions with any systemic reaction (~60 %) and SAEs (<0.5 %) were comparable between vaccine and placebo recipients [33]. Smaller studies in females from Mexico and Korea reported similar frequencies of local and systemic AE [24, 34]. An open-label study in Vietnam comparing four 4vHPV vaccine dosing schedules found slightly lower rates of injection site pain (<69 % for any vaccine dose/schedule) [22]. With respect to age, in one trial a significantly lower proportion of younger (10–15 years) compared with older (16–23 years) females reported injections site pain (79 versus 86 %) and redness (20 versus 26 %). However, more younger females reported fever (12 versus 7 %) [27]. In a study of 4,000 older women (24–45 years) safety was comparable to younger females, with modestly lower frequencies of both local and systemic reactions [35, 36].

The 4vHPV vaccine was evaluated in a head-to-head comparison study between boys and girls aged 10–15 years in which local and systemic events were comparable between genders [27]. In one study of 4,000 males aged 16–26 years, ISRs were significantly more common among 4vHPV vaccine compared with aluminium-containing placebo recipients (60 versus 54 %) [37]; however, severe pain was uncommon in either group [17]. These frequencies were lower than reported among females in trials of similar design. Reporting of SAEs and new medical conditions was comparable between male vaccine and placebo recipients [17, 37], and safety in men who have sex with men, a subset of all males in these studies, was consistent with that for the whole study population [37]. Among subjects seropositive at baseline for at least one vaccine HPV type, the proportions reporting injection site reactions were similar to that of all subjects, and in both females and males [28, 29, 37].

When specifically reported, the frequency and severity of AEs following subsequent 4vHPV vaccine doses appeared similar, if not reduced, compared with AEs after the first dose [28, 29]. Two small studies in young females noted a decreasing proportion of recipients reporting injection site pain but increasing proportions reporting erythema and swelling with subsequent doses [27, 30]. Another study reported fewer participants with fever after each dose (5.1, 4.3 and 2.6 % following doses 1, 2 and 3 respectively) [24]. In males there was no increase, and suggestion of some decrease, in ISR and systemic adverse events with successive doses [37]. One small study reported a small increase in reactogenicity when more than three doses of vaccine were given; adverse events occurred in 80 % of women after a fourth dose at month 60 compared with 65.5 % after dose 3 at month 6. However, the majority of AEs were mild to moderate [38].

Studies of concomitant vaccination have generally demonstrated no or little change in the AE profile for the 4vHPV vaccine [30, 39–41]. For example, adverse reactions in adolescents given the 4vHPV vaccine concurrently with the hepatitis B vaccine, or alone, were comparable [41]. A modestly higher proportion of adolescents (4 %) reported ISR from 4vHPV and some systemic reactions (8 % more with headache) after concurrent administration of 4vHPV vaccine with the diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis (dTpa-IPV) vaccine [40].

3.2 Summary for 2vHPV from clinical trials

The safety profile from clinical studies of the 2vHPV vaccine appears generally consistent with that for 4vHPV vaccine. A pooled analysis of 11 studies in about 30,000 females aged ≥10 years (with approximately 16,000 receiving at least one dose of 2vHPV and almost 46,000 vaccine doses administered) showed a higher incidence of ISR (pain, redness, swelling) in 2vHPV vaccine recipients compared with controls given an aluminium-containing control vaccine or hepatitis A vaccine [42]. The published trials within this review reported similar safety outcomes [10, 21, 25, 43–53]. Pain was the most common symptom (approximately 80 %) in all age groups and occurred in up to 97 % of adolescent girls [51]. Severe pain was reported in up to 7.5 % of recipients aged 15–25 years and severe ISR was more common in vaccine recipients (up to 0.6 % for redness and 1.2 % for swelling versus 0.1 and 0.2 %, respectively) [42]. However, ISRs were transient, generally lasting <5 days and mostly 2–3 days [10, 21, 25, 43–53].

Up to 55 % of 2vHPV vaccine recipients reported systemic symptoms, most commonly fatigue, headache and myalgia. Selected systemic symptoms were more common in vaccine recipients compared with control recipients in some, but not all, studies. There were no significant differences in SAEs, unsolicited symptoms and medically significant conditions [42]. Five deaths were reported (1 in a 2vHPV vaccine recipient and 4 in control recipients). However, no deaths were considered related to vaccination [42]. In follow-up studies, over 4 or more years, rates of vaccine-related SAEs, new-onset chronic disease and new-onset autoimmune disease were no different between groups [10, 44, 54, 55]. In addition, the proportions reporting significant medical events were similar among groups when stratified by age [56].

The safety profile of 2vHPV from smaller studies in new settings/populations has been consistent with earlier large studies, albeit with some limitations due to small numbers of participants. These have included studies in Korean girls (aged 10–14 years) [25] and women[46], a phase I study in 30 females in China [23] and a study in 50 girls aged 9–13 years in Bangladesh [45].

The frequency of ISR following 2vHPV vaccination, as well as systemic symptoms, appeared to diminish with increasing age among females [51], although in one study the AE profile was similar in those aged 10–14 and 15–25 years, respectively [49]. One study compared the three-dose schedule of the 2vHPV vaccine with two-dose schedules using the standard or double-strength formulations of the 2vHPV vaccine among women aged 9–25 years [57]. The AE profile over a 2-year follow-up period did not differ between the four groups, including those receiving the higher antigen content vaccine doses [57]. There is only one published trial of the use of 2vHPV vaccine in males and this did not include direct comparison with females. However, the AE profile reported in males was consistent with that from female studies [50].

Rates of AEs following concurrent administration of the 2vHPV vaccine with other vaccines (diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine, diphtheria-tetanus-acellular pertussis vaccine, meningococcal conjugate vaccines, hepatitis B vaccine and the combined hepatitis A/hepatitis B vaccine) were generally comparable to those of participants given the 2vHPV vaccine alone [58–61] and similar to those for the 2vHPV vaccine administered alone in other studies. There was no increase in the frequency of solicited local or systemic adverse events with subsequent doses in the three-dose course of the 2vHPV vaccine, irrespective of whether the vaccine was administered alone [42, 48, 49] or concurrently with other vaccines [58, 61].

The 2vHPV vaccine contains a unique adjuvant called ASO4. A study investigating autoimmune diseases in all individuals enrolled in randomised, controlled trials of ASO4-containing vaccines ($n = 68{,}512$) over a mean follow-up period of 21 months found an overall rate of around 0.5 % for autoimmune events that did not differ between the AS04 and control groups [62]. The relative risk of an autoimmune event was 0.92 (95 % CI 0.70, 1.22) for the HPV 16/18 vaccine specifically.

3.3 Meta-Analyses of Clinical Trials

A number of meta-analyses of safety data from clinical trials of HPV vaccines have been conducted. One study [63] included data from six randomised controlled trials conducted up to June 2007 involving 2vHPV [44, 48, 52] and 4vHPV vaccines [12, 28, 29, 31], as well as the prototype monovalent type 16 HPV L1-VLP vaccine [64] in comparison with various controls. In the 40,323 female participants aged approximately 15–25 years, the incidence of SAEs in the vaccine and control groups was similar (odds ratio 0.998, 95 % CI 0.87–1.14). From four major studies that reported on death following HPV vaccine administration (two each for 4vHPV and 2vHPV), a total of ten deaths occurred in vaccine recipients and 11 deaths in control recipients (odds ratio 0.91, 95 % CI 0.39–2.14). No deaths were considered attributable to vaccination [63]. A more recent meta-analysis [65] that pooled data from seven unique clinical trials [10, 12, 28, 29, 31, 36, 44, 48, 52, 64, 66–68] involving 44,142 females given either 2vHPV or 4vHPV (or control/placebo) vaccines found no increase in the risk of SAEs among vaccine recipients (risk ratio 1.00; 95 % CI 0.91–1.09). There was a trend, which did not reach statistical significance, toward an increased risk of injection site-related SAEs among vaccine compared with control recipients (risk ratio 1.82; 95 % CI 0.79–4.20) [65].

3.4 Comparing 2vHPV Vaccine and 4vHPV Vaccine Based on Clinical Trials

One observer-blinded randomised head-to-head study compared 2vHPV and 4vHPV vaccines directly [69]. In the approximately 1,100 women aged 18–45 years, solicited AEs were significantly more common in 2vHPV compared with 4vHPV vaccine recipients: 95.1 % (95 % CI 92.8–96.7 %) versus 85.1 % (95 % CI 81.8–88.1 %), respectively [69]. Injection site pain, redness and swelling, and fatigue and myalgia were more common in 2vHPV vaccine recipients, as was severe ISR [17.4 % (95 % CI 14.2–20.9 % for 2vHPV) and 3.4 % (95 % CI 2.0–5.4 %) for 4vHPV, respectively]. However, overall most AEs were transient and of mild or moderate severity. At 24-month follow-up, the proportions reporting SAEs, significant medical conditions, new onset chronic diseases or autoimmune diseases were similar between the two groups

[70]. Of note, and possibly related to the propensity for more ISR following 2vHPV, the magnitude of the immune responses to each vaccine across all age strata was generally greater for 2vHPV. For example, geometric mean titres of serum neutralizing antibodies were 2.3–4.8-fold higher for HPV-16 and 6.8–9.1-fold higher for HPV-18 after 2vHPV compared with 4vHPV [69]. The higher ISR rates among 2vHPV vaccine recipients seen in this study needs to be considered against this evidence for better immunogenicity, although the clinical significance of the latter is not known. The safety results of this single head-to-head study are generally consistent with that from separate studies of both vaccines.

In summary, all randomised clinical trials of both 2vHPV and 4vHPV vaccines provide evidence of an excellent safety profile. Although both vaccines were associated with relatively high rates of ISR, particularly pain in most participants, when compared with either control vaccine or ISR reported for other routinely administered vaccines, these reactions were predominantly of short duration and resolved spontaneously. Systemic adverse events, such as headache and malaise, did not consistently occur more often in HPV vaccine recipients and the incidence of serious adverse events, including new onset chronic conditions and deaths, was not different in HPV vaccine recipients than in controls subjects. Whilst these data are robust, there are limitations inherent in clinical trials and meta-analyses. They are not powered to assess differences in specific chronic and/or autoimmune conditions, proposed as being potentially vaccine-related, and are not conducted in persons wholly representative of the population (for example by ethnicity or underlying medical conditions). As such, post-licensure studies in large populations have been important (discussed in Sect. 5.4).

4 Safety of HPV Vaccines During Pregnancy

HPV vaccines are not recommended for use in pregnant women and pregnant subjects were excluded from participating in the clinical trials of both HPV vaccines. However, some participants did become pregnant despite using contraception and undergoing pregnancy testing prior to dose administration. The relatively large number of pregnancies that occurred, the prospective nature of the studies, control groups and documentation of outcomes make these clinical data very valuable [71]. Pregnancy outcomes for vaccine trial participants were reported irrespective of the relationship between conception and dose/s, but also separately for participants who conceived within either 30 or 90 days of vaccination. For the majority of pregnancies, vaccination did not occur during the period when any theoretical risk would be most biologically plausible (close to the time of conception or during early embryogenesis). Thus, these studies are still limited by their small sample size. Following vaccine registration, pregnancy registries for both vaccines have been established [72, 73]. These registries collect spontaneously reported cases of exposure, which can assist in detection of a significant concern. However, they also have many limitations, such as limited knowledge of precise gestational age at time of exposure, selective reporting, underreporting, inability to calculate reporting rates (in vaccinated and unvaccinated individuals) and representativeness (in comparison with the overall pregnant population).

4.1 The 4vHPV Vaccine and Pregnancy

Overall, the proportions of pregnancies that resulted in an adverse outcome (spontaneous abortion, late foetal death, infant with congenital anomalies) among the 4vHPV vaccine and control recipients who became pregnant at any time during the clinical trials course (13–16 % of >12,000 participants aged 15–26 years) were similar [74]. In one study, where 70 women were vaccinated within 30 days of conception, there were 5 cases of congenital abnormalities in infants of vaccine recipients compared with none among 66 women who received aluminium-containing placebo, with a statistically significant risk difference (4.5; 95 % CI 1.1–10.1) [28]. However, those abnormalities were relatively common and unrelated: hip dysplasia, congenital ankyglossia/congenital pyloric stenosis, congenital hydronephrosis, congenital megacolon and talipes. A subsequent pooled analysis of five phase 3 clinical trials, for outcomes following vaccination within 30 days of conception, identified no additional cases among vaccine recipients but one infant with congenital anomalies born to a placebo recipient. This rendered the risk difference statistically insignificant [74]. Over all time periods, the number of infants with congenital anomalies was not statistically different between the vaccine and placebo groups (40 versus 30; 2.0 versus 1.5 %, $p = 0.20$) and rates were consistent with those expected. Although generally reassuring, caution in drawing firm conclusions from this pooled analysis is warranted, in part because of various methodological limitations, particularly post-hoc pooling of studies of different design [71].

Post-licensure data on pregnancy outcomes reported to the pregnancy registry for 4vHPV established by the manufacturer are published covering a 2-year period [75]. These included 517 prospectively followed pregnancies, with 451 (87.2 %) resulting in live births, including three sets of twins [72]. Of these HPV vaccine-exposed neonates

439 (96.7 %) were normal. The rates of spontaneous abortions [6.9 per 100 outcomes (95 % CI 4.8–9.6)] and major birth defects were not greater than unexposed population rates. The prevalence of major birth defects was 2.2 per 100 live-born neonates (95 % CI 1.05–4.05). The registry also received reports of two cases each of the rare conditions anencephaly and schizencephaly (one reported prospectively and one retrospectively for each condition) in infants whose mothers received the vaccine within 2–21 days after the last menstrual period [72]. The estimated population prevalence of these two conditions was 1.1 per 100,000 births and 1.5 per 100,000 births, respectively, but because of the limitations discussed above, incidence rate estimates in the vaccinated population cannot be calculated. Detailed annual reports from this registry can be obtained on request. The most recent contains data on approximately 1,500 pregnancies prospectively followed to May 2011 and does not indicate a causal relationship between 4vHPV and adverse pregnancy outcomes [75].

4.2 The 2vHPV Vaccine and Pregnancy

Similar to 4vHPV, there are no specific studies of the use of 2vHPV in pregnant women. Published studies reporting on pregnancy outcomes in 2vHPV clinical trial participants predominantly focussed on miscarriage (spontaneous abortion) rates. A combined analysis from two double-blind randomised controlled trials of 2vHPV found that among >26,000 women aged 15–25 years there were 3,599 pregnancies eligible for analysis [76]. The 2vHPV vaccine was not associated with an increase in the risk of miscarriage compared with the control hepatitis A vaccine (11.5 versus 10.1 %, respectively), and rates of miscarriage were not different from that expected. In women who conceived within 90 days after receiving a vaccine or placebo dose ($n = 230$), a non-significant increased rate in miscarriage in the 2vHPV vaccine recipients was observed (13.7 versus 9.2 %, $p = 0.033$ by permutation test) [76].

Another pooled analysis, which included participants of one of the two studies above, found that in 415 participants who became pregnant around the time of vaccination spontaneous abortion rates varied between 2vHPV and control recipients, being higher among younger 2vHPV vaccine recipients [11 % compared with those who received aluminium-containing placebo (8.3 %) or hepatitis A vaccine (5.8 %)], but lower among older 2vHPV compared with placebo recipients [42]. Rates of pregnancy resulting in premature delivery did not differ substantially. Data on congenital anomalies were not reported in these published studies [42]. A vaccine registry for 2vHPV [77] has also been established, but no published data from the registry are available.

4.3 Conclusion Regarding Use of HPV Vaccines in Pregnant Women

In summary, pregnancy adverse outcomes in both 4vHPV and 2vHPV studies appeared similar overall among vaccine compared with control recipients and were comparable to population rates. Evidence for an epidemiologic association of infant congenital anomalies or miscarriage with receipt of a dose of either vaccine at any time, including close to conception, has not been established from the available clinical trial and post-licensure data. However, as discussed above, these studies have limitations, and additional data from population-based data linkage studies of pregnancy outcomes in vaccinated women, would be valuable. For example, a study of ASO3-adjuvanted pandemic influenza vaccine in Denmark demonstrated no difference in pregnancy outcomes in vaccinated compared with unvaccinated women [78]. Immunisation guidelines recommend that pregnant women should avoid vaccination until after delivery [16, 79, 80]. Women inadvertently vaccinated whilst pregnant, or who conceive shortly after vaccination, can be reassured there is no evidence to indicate need for medical termination of pregnancy [16, 79].

5 Post-Licensure Experience

Although safety is one of the primary outcomes measured in vaccine clinical trials, the number of participants included and short follow-up periods are limitations [81] that inherently restrict the identification of rare adverse events [18]. Clinical trial participants are often homogenous with regards to age, ethnicity and health status and hence trial results are not always generalisable to the populations in which vaccines will be introduced. Post-licensure surveillance is essential to detect rare or unexpected adverse events and to monitor safety in large diverse populations under variable real-life conditions. Many post-licensure assessments of HPV vaccine safety have been performed and are discussed below [18, 82].

5.1 Passive Surveillance

Some countries have passive reporting systems for AE related to medicines and vaccines in which information is spontaneously reported by health practitioners or the public rather than systematically sought out. These include the UK Yellow Card scheme (medicines and vaccines) [83], and others specifically for vaccines, including the US Vaccine Adverse Event Reporting System (VAERS) [84], and the Canadian Adverse Events Following Immunisation Surveillance System (CAEFISS) [85–87]. Reports of

adverse events following immunisation (AEFI), in addition to medicines, are also collected via Vigibase, the World Health Organisation's programme, from multiple countries [88]. However, these systems have inherent limitations including: capture of only a small proportion of total adverse events; great variation in reporting frequency, quality and completeness; lack of timely accurate data on vaccine usage (estimates of incidence rates calculated on all doses distributed rather than by age stratified data on doses administered); lack of detailed clinical data required to assess causality; and recording of all events independent of whether a causal association with the vaccine administered exists [89]. Identification of safety signals for unexpected or previously unknown events may arise [90]; however, determining causality is often difficult [91] and usually requires further evaluation using additional surveillance and epidemiological studies [92].

Published national passive surveillance data for HPV vaccination are available from Australia, the Netherlands, USA and UK [93–96]. As expected, reporting rates differ (Table 1) because of differences in reporting mechanisms, case definitions and how rates are derived. For example, by the end of 2008, the US VAERS received 12,424 reports of adverse events following more than 23 million doses of the 4vHPV vaccine distributed, giving an overall reporting rate of 539 reports per million doses distributed [94]. In comparison, reporting rates for adverse events following 4vHPV in Australia were 249 per million doses distributed, but were higher (~400 per million) if limited to school girls only [97, 98]. With 2vHPV, higher reporting rates for adverse events were seen in the UK (1,045 per million doses administered) and in the Netherlands following a vaccination campaign for girls 12–16 years of age (1,160 per million doses administered); however, this may represent system differences rather than differences in AE rates per se. [95, 99]. Reporting rates cannot be calculated for data from multiple countries using WHO's Vigibase because of the lack of data on doses distributed or administered [99].

The majority of AEFIs with the HPV vaccination reported via passive surveillance have been minor and align with expected adverse events seen in pre-licensure clinical trials. The most commonly reported AEFI included injection site reactions, headache and dizziness [93–96, 100]. Only a small and expected proportion of AEFIs were categorised as 'serious', for example, 7 % of all reports to VAERS [101]. The majority of reported events to date are in females: in the 2 years after the 4vHPV vaccine was registered in males in the US, there were 504 male reports made to VAERS (6.5 % considered serious). The most common non-serious adverse events reported by males were similar to females and included dizziness, syncope and injection site pain [101].

A myriad of more serious adverse events following HPV vaccination have been reported to passive surveillance systems, including anaphylaxis, Guillain-Barré syndrome, transverse myelitis and thromboembolic events [94]. Comparisons of observed versus expected incidence rates of disease in a population are subject to the limitations of the passive reporting systems discussed above and the availability of data on background rates for a specific condition. Thus, enhanced passive and/or active surveillance to detect specific adverse events and/or to investigate signals derived from passive surveillance have been conducted or are ongoing. As discussed below, such studies utilise accurate data on vaccines administered and can better establish risk of HPV-vaccine attributable AE [82].

No deaths reported and published in passive surveillance systems data have been attributed as causally related to either of the HPV vaccines [93, 96, 101]. The importance of thoroughly investigating deaths that occur shortly after vaccination to determine potential alternative causes was highlighted by a much publicized case in the UK, where a teenage girl died suddenly on the same day of vaccination from a previously undetected tumour [102]. The propensity to assume causality with serious outcomes was also poignantly highlighted when a HPV demonstration project in females in India was suspended because of the occurrence of four deaths temporarily related to vaccination [103]. Although the deaths have been reportedly found to be unrelated to vaccination, loss of confidence in HPV vaccination led to the suspension of clinical studies of HPV vaccine in India [104].

5.2 Case Reports and Case Series

When a vaccine is first licensed, publications of AEFI reports from individuals or groups of individuals are common. However, such 'case reports' can only rarely provide strong evidence of a causal link with vaccination, typically when the AE that occurs is directly related to the vaccine (for example, injection site reactions or isolation of a neuropathic vaccine-derived poliovirus from a recently vaccinated patient with paralytic poliomyelitis). Even if such reports, together with other scientific data, present credible "mechanistic" evidence of the possibility of a vaccine causing the adverse event, the frequency at which these events occur in relationship to vaccination or in the absence of vaccination (that is, the epidemiologic evidence) will not be available from such studies [105].

Table 2 lists published case reports/case series of AEs following HPV immunisation. Of these, five describe a case or cases of local/regional reactions related to the injection site. Such reports may highlight the occurrence of vaccine delivery errors, the need for improvement in vaccine administration techniques and/or important

Table 1 Reporting rates for adverse events following HPV vaccination from passive safety surveillance systems

Period	Surveillance system/setting	Vaccine	Measured outcome	Reporting rates per 100,000 doses distributed (unless otherwise specified[a,c])	References
Australia					
April 2007–June 2010	TGA (national)	4vHPV	Any AEFI	24.9[b]	[93]
			Anaphylaxis	0.26	
			Fainting	2.2[b]	
April 2007–August 2009	TGA (national)	4vHPV	Any AEFI	24.0	[136]
			Anaphylaxis	0.25	
2007	School-based cohort (2 states: Vic, South Australia)	4vHPV	Hypersensitivity (suspected)	9.2[a,b] (all rates per doses administered)	[98]
			Hypersensitivity (probable)	0.8[a,b]	
			Anaphylaxis	0.5[a,b]	
2007	School-based cohort (1 state: NSW)	4vHPV	Any AEFI	41.0[a] (all rates per doses administered)	[97]
			Anaphylaxis (suspected)	4.5[a]	
			Anaphylaxis (probable)	2.6[a]	
May 2007–April 2009	SAEFVIC (1 state: Victoria)	4vHPV	Any AEFI	40.4[b]	[127]
			Fainting	7.8	
2010 and 2011	12–17 year olds (1 state: NSW)	4vHPV	Any AEFI	14.1 (2010)[a] (all rates per doses administered)	[137, 138]
				37.9 (2011)[a]	
Europe					
2009	RIVM (national, The Netherlands)	2vHPV	Any AEFI	116.0[a] (all rates per doses administered)	[95]
			Fainting	10.0[b]	
			Anaphylaxis	No cases reported	
April 2008–July 2010	Yellow cards (national, UK)	2vHPV	Any AEFI	104.5[a] (all rates per doses administered)	[96]
			Psychogenic events (including fainting)	19.8[a,b]	
			Anaphylaxis	1.0[a,b]	
USA					
June 2006–Dec 2008	VAERS (national, USA)	4vHPV	Any AEFI	53.9	[99]
			Fainting	8.0[b]	
			Anaphylaxis (serious only)	0.03[b]	
June 2006–Sept 2009	VAERS (national, USA)	4vHPV	GBS	0.80[a]	[131]
			GBS (6 weeks after vaccination)	0.07[a,c]	
June 2006–December 2008	VAERS (national, USA,)	4vHPV	Any AEFI	53.9	[94]
			Fainting	8.2	
			Anaphylaxis	0.1	
			Hypersensitivity	3.1	

[a] Reporting rate calculated based on number of vaccine doses administered

[b] Reporting rates calculated based on values provided in manuscript

[c] Weekly reporting rates (per week per 100,000 patients)

Table 2 Published case series/case reports of adverse events following HPV immunisation

References	Country	Vaccine	Condition	Summary of case details	Comments
Local/regional reactions					
[139]	USA	4vHPV	Unilateral cervical and supraclavicular lymphadenopathy	A 26-year-old woman day 3. Same side as injection and no other symptoms/signs. Dose 1 only	Contemporaneous VAERS search by authors found 55 non-confirmed reports of lymphadenopathy post HPV vaccine
[140]	Belgium	4vHPV	Brachial plexus neuritis	A 19-year-old woman onset 1 month post dose 2 same side as vaccination. Surgery opposite wrist 2 months prior	Contemporaneous VAERS search by authors found 4 non-confirmed reports post HPV vaccine
					Aetiology unknown. Associated with surgery, infection, autoimmune disease and vaccination in preceding 3–14 days
[141]	USA	4vHPV	Aluminium granuloma	A 26-year-old woman, tender nodule outer left arm 2 months post dose 3	History of granulomatous appendicitis, raises question of alternative aetiology for granulomatous disease
[107]	Australia	4vHPV	Localised lipoatrophy	Two cases aged 23 and 25 vaccinated with three doses over 6 months	Contemporaneous VAERS search by authors found 11 non-confirmed reports of injection site atrophy post HPV vaccine
					Uncommon condition. Often idiopathic but can be due to local trauma, inflammatory conditions and injections of drugs including whole cell pertussis vaccine
[106]	Australia	4vHPV	Complex regional pain syndrome	Four females (aged 12–16 years) developed persistent pain in extremity/ies disproportionate to inciting event (vaccination)	Uncommon condition. Syndromic diagnosis. Behavioural and physical therapy optimal
					Time to complete resolution varied from 5 days–7 months
Systemic reactions					
[20]	Australia	4vHPV	Mass psychogenic response	26 school girls sought care in their school clinic after vaccination for a variety of symptoms (dizziness, palpitations, weakness). 4 girls presented to hospital emergency department	None identified to have organic cause after extensive medical investigation
[142]	Australia	4vHPV	Pancreatitis	A 26-year-old woman 4 days post dose 1	Pancreatitis incidence 25 per 100,000 in women 25–29 years in Australia
				No cause identified	Multiple causes, 10 % idiopathic
[143]	Austria	2vHPV	Acute disseminated encephalomyelitis (ADEM)	A 15-year-old girl 23 days post dose 2	
[109]	Australia	4vHPV	Acute disseminated encephalomyelitis (ADEM)/multiple sclerosis	Five patients aged 16-25 with clinical presentation of ADEM or MS between 1 to 21 days post dose 2 or 3	Three patients had prior demyelination episodes
					MS incidence 6 per 100,000 in women 20-29 years in Australia. Peak in young women
[144]	Germany	4vHPV	Acute disseminated encephalomyelitis (ADEM)	A 20-year-old woman within 28 days of dose 2	

Table 2 continued

References	Country	Vaccine	Condition	Summary of case details	Comments
[145]	USA	4vHPV	Acute disseminated encephalomyelitis (ADEM)	A 16-year-old 10 days post dose 2	
[146]	USA	N/S	Fulminant myocarditis	A 17-year-old 1 week post dose 1	Major cause of sudden death in children and young adults
[147]	USA	4vHPV	Multiple sclerosis first presentation	Two young women approx. 1 month post vaccine	
[148]	USA	4vHPV	CNS demyelination. First presentation of MS	Two women aged 19 and 18. Onset 1 month post dose 2 and 6 weeks post dose 1	
[149]	USA	4vHPV	Postural tachycardia syndrome	A 20-year-old 2 weeks post dose 3	Pathogenesis uncertain, may have autoimmune aetiology. Increased prevalence in young women
[150]	USA	4vHPV	Ampiginous choroiditis	A 17-year-old 3 weeks post dose 1	Rare bilateral aggressive posterior uveitis
[151]	USA	4vHPV	Opsoclonus myoclonus	An 11-year-old 15 days after dose 1 developed moodiness. One month later eye symptoms developed. Deterioration 4 days post dose 2 with ataxia and myoclonus	Rare neurological condition. Paraneoplastic syndrome in 50–60 % cases. Autoantibodies detected that target the cerebellum
[152]	Italy	2vHPV	Telogen effluvium	Two patients 11 years of age with loss of hair post dose 2. Worsened post dose 3 then gradually resolved	
[153]	Italy	2vHPV	Bilateral papilloedema	An 11-year-old girl 10 days post dose 2	Laboratory studies did not support vaccination as the cause
[154]	France	4vHPV	Immune thrombocytopenic purpura	A 16-year-old 3 months post dose 2	
[155]	Philippines	N/S	Systemic lupus erythematosus	Three cases reported: a 17-year-old with onset 2 months post dose 2; 45 year old (past history of rheumatoid arthritis) 4 months post dose 2. 58 year old flare of long-standing SLE 3 months post dose 2	

N/S vaccine type not specifically stated, however, presumed to be 4vHPV

Table 3 Post-licensure studies of adverse events following HPV vaccine using enhanced passive surveillance methods

Population/setting	Vaccine	Methods of evaluation	Outcome reported after HPV	References
The Netherlands 2009	2vHPV	Web-based survey on ISR and systemic reactions within 7 days after each vaccine dose	92 % reported ISR (post dose 1)	[156]
HPV catch-up cohort girls aged 13–16 years ($n = 4,282$)		74 % overall response rate (29 % for all 3 doses)	Lower odds of ISR after dose 2 and 3 compared with dose 1 (OR 0.33; 95 % CI 0.28–0.38 and OR 0.43; 95 % CI 0.37–0.51, respectively)	
			92 % reported systemic AE post dose 1, especially myalgia, fatigue and headache. Lower proportion post doses 2 and 3. Systemic AE more frequent in older girls	
			Girls with headache/cold/flu symptoms prior to vaccination had increased rates of ISR and systemic AEs	
			15 % used analgesics post dose 1	
			1.5 % consulted a medical practitioner post dose 1	
			No hospitalisations occurred	
Nepal 2008 secondary school girls aged 10–26 years ($n = 1,096$)	4vHPV	Not stated	7.8 % reported pain at injection site (with any dose)	[113]
Italy 2008–2010 cohort of girls aged 12–26 years in two regions ($n = 4,643$)	2vHPV	Questionnaire-based survey (66 % response rate for dose 1, lower for subsequent doses)	68 % reported pain at injection site	[114]
			26 % reported fatigue	
			17 % reported headache	
			0.5 % reported urticaria ($n = 33$)	
			Syncope (9/7,107 = 1.3 per 1,000 doses)	
			No serious AEs reported	
USA 2008 females aged 11–26 years post dose 1 ($n = 899$)	4vHPV	Questionnaire on AE and attitudes (27 % response rate)	78 % reported pain at injection site	[115]
		Data extracted from electronic medical records	1 % reported syncope, 15 % "pre-syncope"	

Table 4 Post-licensure population-based studies of adverse events following HPV vaccine

Setting/ period	Vaccine	Study cohort	Measured outcome	Main finding	References
UK/ Ireland 2008–2009	2vHPV	Children <16 years with suspected anaphylaxis following vaccination reported to British Paediatric Surveillance Unit (BPSU) >2 million doses administered	Anaphylaxis following HPV (and other) vaccines	Low incidence estimated at 1.4 cases/million doses	[116]
France 2007	2vHPV/ 4vHPV	~5.8 million adolescents and young women; 15.6 % had received ≥1 dose of HPV vaccine (French national healthcare insurance database)	8 pre-specified autoimmune disorders[d]	No signal for autoimmune disorders with HPV vaccination	[123]
USA 2006–2008	4vHPV	~190,000 females aged predominantly 9–26 years who received at least one dose of HPV vaccine (2 managed care organisations)	16 pre-specified autoimmune conditions with new onset within 180 days post each HPV vaccine dose[a]	No evidence of safety signal for autoimmune conditions following 4vHPV vaccination. The IRR for Hashimoto's thyroiditis was significantly elevated but further investigation suggested no relationship[b] Vaccination with 4vHPV associated with syncope occurring on the same day of vaccination and 'skin infections' (likely representing ISR) within 2 weeks following vaccination. No other safety concerns detected	[119]
USA 2006–2008	4vHPV	~190,000 females aged predominantly 9–26 years who received at least one dose of HPV vaccine (2 managed care organisations)	Emergency department visits and hospitalisations within pre-defined risk periods for multiple conditions detected using 265 diagnostic codes		[122]
USA 2006–2009	4vHPV	Females aged 9–26 years, administered >600,000 HPV vaccine doses (7 managed care organisations)	Eight pre-specified well-defined and severe adverse events following HPV vaccine[c]	No statistically significant increased risk for any of the pre-specified adverse events detected Possible association with VTE in girls 9–17 years, however, all confirmed cases had other risk factors	[120]
USA 2006–2009	4vHPV	Females aged 9–26 years in US Vaccine Safety Datalink (VSD) (9.2 million people annually in 8 managed care organisations)	Eight pre-specified well-defined and severe adverse events following HPV vaccine[c]	No statistically significant increased risk for any of the pre-specified adverse events detected Potential signals identified for HPV vaccine with appendicitis and allergic reactions in first 2 week of data collection. RR decreased to null in later weeks	[121]
USA 2005–2008	4vHPV	Retrospective cohort of 12.6 million adolescents/young adults (11–21 years) in five US healthcare plans	Guillain-Barré syndrome following meningococcal conjugate vaccine Secondary outcome: GBS after other vaccines, including 4vHPV	Two cases of GBS observed within 6 weeks of HPV vaccine (584,458 doses) compared with 0.37 expected. Could not exclude risk, although study not designed to make definitive conclusion for HPV vaccination	[117]
USA 2000–2009	4vHPV	1.8 million children aged up to 17 years (5 managed care organisations)	Immune thrombocytopenic purpura (ITP) following different vaccines	No elevated risk following HPV vaccination	[118]

[a] The conditions were: (1) rheumatologic/autoimmune disorders, including immune thrombocytopenia (ITP), autoimmune haemolytic anaemia, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and juvenile rheumatoid arthritis (JRA), (2) autoimmune endocrine conditions, including type 1 diabetes, Hashimoto's disease and Graves' disease and (3) autoimmune neurological/ophthalmic conditions, including multiple sclerosis (MS), acute disseminated encephalomyelitis, other demyelinating diseases of the central nervous system, vaccine-associated demyelination, Guillain-Barré syndrome, neuromyelitis optica, optic neuritis and uveitis

[b] Onset of thyroiditis symptoms occurred prior to vaccination in a number of patients who had received a recent HPV vaccine

[c] Pre-specified adverse events were: Guillan-Barré syndrome (GBS), stroke, venous thromboembolism (VTE), appendicitis, seizures, syncope, allergic reactions and anaphylaxis. Pre-specified post-vaccination periods of risk varied by condition

[d] Eight pre-specified autoimmune disorders (rheumatologic, endocrinologic and neurologic conditions) were considered but not stipulated in the abstract

management issues, for example, the need to avoid repeated vaccination into the same site at which lipoatrophy has occurred or to institute prompt multi-modal therapy for complex regional pain syndrome [106, 107]. However, other reports describe occurrences of serious or striking disease onset for conditions whose aetiology and/or pathogenesis is uncertain. It is well recognised that reporting and attribution of such cases to vaccination can be anticipated when a new vaccine is introduced into a population, particularly where large-scale programmes with high coverage and multiple vaccine doses are implemented [108]. However, implicating vaccines as a causal factor for such diseases, for example multiple sclerosis [109], requires more than a temporal association. Analysis of disease rates between vaccinated and unvaccinated individuals, a consistent temporal relationship, biological plausibility and lack of alternative aetiology are essential factors to be considered [105, 108]. Population-based studies and other evidence available to date, discussed more below, provide evidence that autoimmune diseases are not triggered by HPV vaccination.

Table 2 also contains reference to other events found not to be biologically related to vaccination, such as the occurrence of a "mass psychogenic" response to vaccination among girls in a school-based vaccination clinic in Australia. This report highlighted that factors other than the vaccine constituents, such as the fear of painful events, can trigger adverse reactions to vaccination [20, 110]. Expert review of unusual and serious conditions that occur after vaccination, such as that conducted in specialised immunisation adverse event assessment clinics, is important [111, 112].

5.3 Enhanced Passive and Active Surveillance

Table 3 describes four post-licensure studies that used survey methods to investigate adverse reactions following HPV vaccination predominantly in teenage girls in four different settings: the Netherlands and Italy (2vHPV) and the USA and Nepal (4vHPV). The quality of these studies, particularly the response rate, varied. Overall, the rates of ISR and systemic reactions reported following vaccination were similar to that seen in randomised controlled clinical trials, with the exception of the limited data from the study in Nepal [113], where only 8 % of girls reported pain at the injection site following 4vHPV. The methods of data collection were not presented in this study and it appears likely that methodological and socio-cultural factors may have limited perception and/or reporting of pain.

The most comprehensive study was in the Netherlands, where 4,248 girls aged 13–16 years (74 % of those approached) responded [95]. Participation rates declined progressively after the first, second and third doses of vaccine were received; however, overall no unexpected or SAEs were reported (Table 3). Reporting rates for ISRs were comparable to those for the 2vHPV vaccine in clinical trials, although a higher proportion of participants subjectively reported "pronounced pain" at the injection site (24, 12 and 15 % by dose, respectively). ISRs and systemic symptoms were significantly less common after second and third doses, although this did not account for factors such as non-completion of vaccine course or the survey. Girls who reported feeling unwell in the week prior to vaccination, or who had a history of certain chronic medical conditions, had a statistically higher likelihood of reporting AEs post-vaccination. In a similar study among Italian school girls, no SAEs were reported [114]. ISRs, myalgia, fatigue and headache were the most common reported symptoms. Pain was more commonly reported after the first dose, whereas rates of other local and systemic reactions were higher after subsequent doses. AEs were less frequently reported than in published clinical trials. A smaller study from the US, with a lower response rate but utilising medical record review to also ascertain AE, found girls reported similar ISRs compared with clinical trial data [115]. This study was notable for high rates ($n = 134$, 15 %) of syncope and dizziness (recorded as "pre-syncope") after vaccination.

5.4 Population-Based Epidemiologic Surveillance

Table 4 lists seven published studies of SAE following HPV vaccination in well-defined large populations. Three of these studies focussed on specific conditions: anaphylaxis [116], Guillain-Barré syndrome [117] and thrombocytopenia [118] in children following vaccination of any type. The other five publications report on observational cohort studies conducted using large healthcare databases in the USA [119–122] or France [123] and examined the incidence of pre-specified new onset conditions following vaccination. The study from France (on 2vHPV vaccine) was presented in abstract format only and could not be fully scrutinised. In the US studies, potential new onset conditions were identified by various methods (including hospital/emergency department discharge diagnosis codes, pharmacy prescriptions and laboratory data) and cases had in-depth clinical review. Comparison with incidence rates in unvaccinated same-age female populations (concurrently or historically) or rates following vaccines other than 4vHPV were made. Two studies report on females aged 9–26 years between August 2006 and October 2009 in the Vaccine Safety Datalink (VSD) cohort, in which a total of 600,558 doses of 4vHPV vaccine were recorded [120, 121]. There was no statistically significant increased risk in vaccine recipients for the outcomes studied [these included GBS, stroke, appendicitis, seizures, allergic reactions,

anaphylaxis, syncope and venous thromboembolism (VTE)]. The other two US studies [119, 122] were based on a cohort of almost 190,000 females aged 9–26 years who had received at least one dose of the 4vHPV vaccine. There was no cluster in the onset of 16 pre-specified new onset autoimmune diseases (NOAID) over an 180-day period in relationship to vaccination, age or dose(s) received [119]. Further investigation of an elevated incidence rate ratio for one of the 16 conditions, Hashimoto's disease, did not suggest a true association, as many of the cases were likely pre-existing at the time of vaccination. A more extensive review of medical attendance for 265 distinctly coded conditions occurring in various plausible risk periods following vaccination indicated that only syncope (on the day of vaccination) and 'skin infections' (likely representing injection site reactions) occurred more commonly after vaccination than during non-exposure periods [122].

With the introduction of new vaccines such as HPV vaccines, where three doses are scheduled over a 6-month period, there will inevitably be the onset of new conditions, including immune-mediated diseases, associated in time with vaccination [124]. Rates of immune-mediated diseases in the female population targeted for HPV vaccination (9–26 years) are relatively high, with disease incidence varying substantially across this age group [124]. For example, the hospitalisation rate for autoimmune conditions in women 19–30 years is up to 389/100,000 [62], and in US women aged 19–28 years diagnoses of thyroiditis and multiple sclerosis are ten times more frequent than in adolescent girls [108]. Studies to determine "background rates" of diseases suggested to be potentially vaccine-attributable have been conducted in some countries, such as Denmark [125] and the US [62, 108], and are key to understanding and addressing vaccine safety concerns when they inevitably arise.

5.5 Conditions of Interest Arising from Post-Licensure Surveillance

5.5.1 Syncope

Disproportionately higher rates of syncope after HPV vaccination compared with that observed in pre-licensure RCTs were reported from post-licensure surveillance in the US [115], Australia [94], the Netherlands [126] and Italy [114]. The reporting rate for syncope (Table 1) following 4vHPV was similar in the USA and the Netherlands and in state-based but not national reports from Australia, at approximately 80–100 per million doses [127]. Although neither dizziness nor syncope was reported at increased rates in vaccine compared with control recipients in pre-licensure studies, given the high overall reporting rate of pain following vaccination, syncope in response to this painful stimulus is not unexpected under real-life conditions. It has become clear that in the adolescent vaccine target population, reports of syncope following any vaccination are common compared with other target groups [128]. In the US, syncope in persons >5 years of age following any vaccination increased from 0.28 per million vaccine doses distributed in 2004 to 0.54 per million doses distributed in 2006 after the introduction of three new vaccines targeted to adolescents: meningococcal conjugate vaccine, reduced dose diphtheria-tetanus-pertussis vaccine and HPV vaccine [129]. Analysis of VSD data found no increased risk of syncope specifically following HPV4 when compared with other vaccines given to adolescents [120]. Syncope can lead to syncopal seizures [127] and falls: about 15 % of syncopal episodes reported to VAERS resulted in a fall, of which 68 % resulted in a head injury [94]. This highlights the importance of practical measures to anticipate and/or avoid syncope and its complications, such as lying down during, and resting after, vaccination [128, 129]. In one Australian review, a majority of patients with HPV vaccine-related syncope or syncopal seizures were re-vaccinated without recurrence [127].

5.5.2 Anaphylaxis

Although considered a rare AEFI, anaphylaxis can occur because of antigen, vaccine adjuvant and/or vaccine excipients [98]. Of note, no cases of vaccine-related anaphylaxis were reported in the phase 3 studies of HPV vaccines, although episodes of immediate and severe allergic reactions (facial oedema, severe bronchospasm) occurred [18]. Reporting rates of anaphylaxis following HPV vaccination have generally been consistent in both national passive surveillance systems and population-based studies (Tables 1, 3) and within the estimated range of that for other vaccines of 1–10 cases per million doses. The exception was one early study from Australia in which higher rates of anaphylaxis (2.6 per 100,000 doses) were reported in a school-based program [97]; this could partly be explained by the different surveillance mechanism and case definitions employed in this study. Of note, the 4vHPV vaccine is produced in a yeast-based (*Saccharomyces cerevisiae*) system and use of this vaccine is contraindicated in persons with a history of immediate hypersensitivity to yeast. The 2vHPV vaccine pre-filled syringes contain latex within the stopper and should not be used in persons with a history of anaphylaxis to latex [130]. Overall, the evidence from post-licensure surveillance suggests that anaphylaxis and serious allergic reactions following HPV vaccination are rare and manageable, consistent with that found for other vaccines. In two retrospective cohort studies in females from Australia, only a proportion of those reported as 'suspected' anaphylaxis

cases were classified as anaphylaxis on clinical review, and even fewer (1/19) were found to have probable hypersensitivity after skin prick testing [97, 98]. The majority of girls with a history of suspected anaphylaxis who were re-vaccinated under close medical observation had no subsequent adverse reactions [98].

5.5.3 Guillain-Barré syndrome (GBS)

A review of GBS cases reported to the US VAERS estimated a 2.5- to 10-times greater rate of GBS within 6 weeks after 4vHPV vaccination compared with that expected in the general population (6.6 events per week per 10 million subjects versus 0.65–2.57 cases per week per 10 million population) [131]. However, the increased propensity to report events that occur in a temporal relationship to vaccination and lack of a control group meant further investigation to better delineate any possible relationship was required. Subsequent population-based studies, employing extensive case finding methods for GBS, have not provided evidence of a rate that is significantly greater than that expected in the adolescent and young adult female population (Table 4) [119, 120].

5.5.4 Venous Thromboembolism (VTE)

A safety signal for VTE was identified following review of VAERS reports to June 2006 [94]. However, of the cases that had sufficient information for review, 90 % had a known risk factor for VTE, such as oral contraceptive use. The time to onset after vaccination was also highly variable [94]. Analysis of VTE in the VSD population-based cohort revealed a non-significant increased relative risk of 1.98 among females aged 9–17 years when compared with historical rates; however, all five cases had known risk factors for VTE [120]. Increased rates of VTE post HPV vaccination have not been reported in other settings, suggesting this is unlikely to be causally related to vaccination.

6 Summary of Findings

A variety of population-based post-licensure studies have assessed adverse events, including those with delayed onset, in females given HPV vaccines. Despite the inevitable publication of case reports raising the potential association between HPV vaccination and a range of severe chronic conditions of poorly defined aetiology such as multiple sclerosis, evidence from these well-conducted population-based studies has consistently not identified any new or concerning safety issues. Randomised controlled clinical trials conducted before vaccine licensure identified that ISR (particularly pain) and mild self-limited systemic symptoms (such as myalgia and headache) occur commonly after HPV vaccination and should be anticipated. One head-to-head comparison study found injection site reactions and some systemic symptoms to be more common in 2vHPV compared with 4vHPV vaccine recipients although, overall, events in most recipients were well-tolerated and self-limiting. Allergic reactions and syncope can occur following HPV vaccination but can be managed with appropriate care [132]. Data from pooled clinical studies of HPV vaccination given inadvertently during pregnancy or near the time of conception have not provided evidence for foetal harm or higher rates of miscarriage; however, advice regarding avoiding vaccination during pregnancy is warranted, given the limitations of such studies.

The findings of this review are consistent with the expert assessment of a number of peak advisory bodies [13, 96, 133]. For example, the Global Advisory Committee of the World Health Organisation found in 2007 and 2008 that current evidence on the safety of HPV vaccines was reassuring [132, 134]. Independent systematic reviews of HPV vaccine safety have also drawn this conclusion [18]. In addition, a recent report by the Institute of Medicine (IOM) summarising evidence for causal relationships between certain adverse events and eight different vaccines, including HPV vaccines, identified acceptable levels of evidence to support a causal relationship between HPV vaccination and anaphylaxis and reported acceptance of a causal relationship with any vaccine injection and syncope [105]. Consistent with the findings of this review, the IOM stated that neither the mechanistic or epidemiologic evidence supported an association of HPV vaccination with other outcomes, such as various new onset chronic diseases.

7 Conclusions and Future Considerations

This overview provides an update of the continually expanding body of evidence regarding the safety profile of the two currently licensed HPV vaccines, 2vHPV (Cervarix®) and 4vHPV (Gardasil®). Both have been well characterised in extensive clinical trials and a range of post-licensure studies, some of the most comprehensive employed for any vaccine. Overwhelming, the evidence supports an excellent safety profile, not unlike the majority of other inactivated vaccines assessed in similar populations.

Ongoing initiatives to assess vaccine safety have been summarised elsewhere [82, 135]. Despite the reassuring evidence to date, safety studies in developing countries that adopt HPV vaccine use, and in specific populations not extensively assessed to date, such as males, are awaited. For example, studies in immunocompromised persons, an

important target group, are limited and should occur. In parallel, research to better elucidate background rates of serious diseases and events that can be coincidentally associated in time with vaccination are essential to inform decision-making around vaccine safety issues as they arise [124] and to avoid a loss of confidence in these potentially life-saving vaccines.

Acknowledgments The authors wish to thank Dr. Rashmi Dixit, formerly of the National Centre for Immunisation Research and Surveillance (NCIRS), for assistance in reviewing some studies. We also thank other NCIRS staff for their assistance: Ms. Catherine King for literature searches and Mr. Edward Jacyna and Ms. Lyn Benfield for assistance with data collection and collation.

Dr. Brotherton was a partner investigator on an Australian Research Council (ARC) Linkage Grant for which CSL Biotherapies was a partner organization

Associate Professor Macartney, Dr. Clayton Chiu and Dr. Melina Georgousakis are employees of the Australian National Centre for Immunisation Research and Surveillance, which receives funding from the Australian Government Department of Health and Ageing and the New South Wales Department of Health. Dr. Brotherton is an employee of the Victorian Cytology Service (VCS), which receives funding from the Victorian Health Department and the Australian Government Department of Health and Ageing.

References

1. Schiffman M, Castle PE, Jeronimo J, et al. Human papillomavirus and cervical cancer. Lancet. 2007;370:890–907.
2. Chaturvedi AK. Beyond cervical cancer: burden of other HPV-related cancers among men and women. J Adolesc Health. 2010;46:S20–6.
3. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.
4. Ferlay J, Shin H, Bray F, et al. GLOBOCAN 2008 v1. 2, cancer incidence and mortality worldwide: IARC CancerBase No. 10. Lyon: International Agency for Research on Cancer, 2010; 2012.
5. Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. Vaccine. 2006;24:S4–15.
6. Weinstock H, Berman S, Cates W Jr. Sexually transmitted diseases among American youth: incidence and prevalence estimates, 2000. Perspect Sexual Reprod health. 2004;36:6–10.
7. Da Ros CT, da Silva Schmitt C. Global epidemiology of sexually transmitted diseases. Asian J Androl. 2008;10:110–4.
8. Harper DM. Currently approved prophylactic HPV vaccines. Expert Rev Vaccines. 2009;8:1663–79.
9. Chen J, Ni G, Liu XS. Papillomavirus virus like particle-based therapeutic vaccine against human papillomavirus infection related diseases: Immunological problems and future directions. Cell Immunol. 2011;269:5–9.
10. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet. 2009;374:301–14.
11. Rowhani-Rahbar A, Mao C, Hughes JP, et al. Longer term efficacy of a prophylactic monovalent human papillomavirus type 16 vaccine. Vaccine. 2009;27:5612–9.
12. Villa LL, Costa RL, Petta CA, et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. Br J Cancer. 2006;95:1459–66.
13. National Advisory Committee on Immunization (NACI). Update on human papillomavirus (HPV) vaccines. Can Commun Dis Rep. 2012;38:1–62.
14. Georgousakis M, Jayasinghe S, Brotherton J, et al. Population-wide vaccination against human papillomavirus in adolescent boys: Australia as a case study. Lancet Infect Dis. 2012;12:627–34.
15. Centre for Disease Control. Recommendations on the use of quadrivalent human papillomavirus vaccine in males—Advisory Committee on Immunization Practices (ACIP), 2011. MMWR. 2011;60:1705–8.
16. Australian Technical Advisory Group on Immunisation of the Australian Government Department of Health and Ageing. The Australian Immunisation Handbook. 10th ed. Canberra: Australian Government; 2013.
17. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. N Engl J Med. 2011;364:401–11.
18. Agorastos T, Chatzigeorgiou K, Brotherton JML, et al. Safety of human papillomavirus (HPV) vaccines: a review of the international experience so far. Vaccine. 2009;27:7270–81.
19. Brotherton J, Deeks SL, Campbell-Lloyd S, et al. Interim estimates of human papillomavirus vaccination coverage in the school-based program in Australia. Commun Dis Intell. 2008;32:457–61.
20. Buttery JP, Madin S, Crawford NW, et al. Mass psychogenic response to human papillomavirus vaccination. Med J Aust. 2008;189:261–2.
21. Konno R, Dobbelaere KO, Godeaux OO, et al. Immunogenicity, reactogenicity, and safety of human papillomavirus 16/18 AS04-adjuvanted vaccine in Japanese women interim analysis of a phase ii, double-blind, randomized controlled trial at month 7. Int J Gynecol Cancer. 2009;19:905–11.
22. Neuzil KM, Canh do G, Thiem VD, et al. Immunogenicity and reactogenicity of alternative schedules of HPV vaccine in Vietnam: a cluster randomized noninferiority trial. JAMA. 2011;305:1424–31.
23. Zhu FC, Li CG, Pan HX, et al. Safety and immunogenicity of human papillomavirus-16/18 AS04-adjuvanted vaccine in healthy Chinese females aged 15 to 45 years: a phase I trial. Chin J Cancer. 2011;30:559–64.
24. Kang S, Kim KH, Kim YT, et al. Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: a randomized, placebo-controlled trial in 176 Korean subjects. Int J Gynecol Cancer. 2008;18:1013–9.
25. Kim YJ, Kim KT, Kim JH, et al. Vaccination with a human papillomavirus (HPV)-16/18 AS04-adjuvanted cervical cancer vaccine in Korean girls aged 10–14 years [Erratum appears in J Korean Med Sci. 2010 Dec;25(12):1831]. J Korean Med Sci. 2010;25:1197–204.
26. Kohl KS, Bonhoeffer J, Chen R, et al. The Brighton Collaboration: enhancing comparability of vaccine safety data. Pharmacoepidemiol Drug Saf. 2003;12:335–40.
27. Block SL, Nolan T, Sattler C, et al. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. Pediatrics. 2006;118:2135–45.
28. Garland S, Hernandez-Avila M, Wheeler C, et al. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356:1915–27.
29. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med. 2007;356:1928–43.

30. Reisinger KS, Block SL, Lazcano-Ponce E, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. Pediatr Infect Dis J. 2007;26:201–9.
31. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial [see comment]. Lancet Oncol. 2005;6:271–8.
32. Block SL, Brown DR, Chatterjee A, et al. Clinical trial and post-licensure safety profile of a prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine. Pediatr Infect Dis J. 2010;29:95–101.
33. Perez G, Lazcano-Ponce E, Hernandez-Avila M, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 virus-like-particle vaccine in Latin American women. Int J Cancer. 2008;122:1311–8.
34. Lazcano-Ponce E, Perez G, Cruz-Valdez A, et al. Impact of a quadrivalent HPV6/11/16/18 vaccine in Mexican women: public health implications for the region. Arch Med Res. 2009;40:514–24.
35. Castellsague X, Munoz N, Pitisuttithum P, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24–45 years of age. Br J Cancer. 2011;105:28–37.
36. Munoz N, Manalastas R Jr, Pitisuttithum P, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24–45 years: a randomised, double-blind trial. Lancet. 2009;373(9679):1949–57.
37. Moreira ED Jr, Palefsky JM, Giuliano AR, et al. Safety and reactogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 viral-like-particle vaccine in older adolescents and young adults. Hum Vaccines. 2011;7:768–75.
38. Olsson SE, Villa LL, Costa RLR, et al. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine. Vaccine. 2007;25:4931–9.
39. Arguedas A, Soley C, Laoiza C, et al. Safety and immunogenicity of one done of MenACWY-CRM and investigational quadrivalent meningococcal glycoconjugate vaccine, when administered to adolescents concomitantly or sequentially with Tdap and HPV vaccines. Vaccine. 2010;28:3171–9.
40. Vesikari T, Van Damme P, Lindblad N, et al. An open-label, randomized, multicenter study of the safety, tolerability, and immunogenicity of quadrivalent human papillomavirus (types 6/11/16/18) vaccine given concomitantly with diphtheria, tetanus, pertussis, and poliomyelitis vaccine in healthy adolescents 11 to 17 years of age. Pediatr Infect Dis J. 2010;29:314–8.
41. Wheeler CM, Bautista O, Tomassini JE, et al. Safety and immunogenicity of co-administered quadrivalent human papillomavirus (HPV) 6/11/16/18 L1 virus like particle (VLP) and hepatitis B (HBV) vaccines. Vaccine. 2008;26:686–96.
42. Descamps D, Hardt K, Spiessens B, et al. Safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials. Hum Vaccines. 2009;5:332.
43. Esposito S, Birlutiu V, Jarcuska P, et al. Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted vaccine administered according to an alternative dosing schedule compared with the standard dosing schedule in healthy women aged 15 to 25 years: results from a randomized study. Pediatr Infect Dis J. 2011;30:e49–55.
44. Harper DM, Franco EL, Wheeler CM, et al. Sustained efficacy up to 4–5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet. 2006;367:1247–55.
45. Khatun S, Akram Hussain SM, Chowdhury S, et al. Safety and immunogenicity profile of human papillomavirus-16/18 AS04 adjuvant cervical cancer vaccine: a randomized controlled trial in healthy adolescent girls of Bangladesh. Jpn J Clin Oncol. 2012;42:36–41.
46. Kim SC, Song YS, Kim YT, et al. Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in 15–25 years old healthy Korean women. J Gynecol Oncol. 2011;22:67–75.
47. Medina DM, Valencia A, de Velasquez A, et al. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine: a randomized, controlled trial in adolescent girls. J Adolesc Health. 2010;46:414–21.
48. Paavonen J, Jenkins D, Bosch FX, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet. 2007;369:2161–70.
49. Pedersen C, Petaja T, Strauss G, et al. Immunization of early adolescent females with human papillomavirus type 16 and 18 L1 virus-like particle vaccine containing AS04 adjuvant. J Adolesc Health. 2007;40(6):564–71.
50. Petaja T, Keranen H, Karppa T, et al. Immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in healthy boys aged 10–18 years. J Adolesc Health. 2009;44:33–40.
51. Schwarz TF, Spaczynski M, Schneider A, et al. Immunogenicity and tolerability of an HPV-16/18 AS04-adjuvanted prophylactic cervical cancer vaccine in women aged 15–55 years. Vaccine. 2009;27:581–7.
52. Harper DM, Franco EL, Wheeler C, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet. 2004;364:1757–65.
53. Petaja T, Pedersen C, Poder A, et al. Long-term persistence of systemic and mucosal immune response to HPV-16/18 AS04-adjuvanted vaccine in preteen/adolescent girls and young women. Int J Cancer. 2011;129:2147–57.
54. Lehtinen M, Paavonen J, Wheeler CM, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial [Erratum appears in Lancet Oncol. 2012 Jan;13(1):e1]. Lancet Oncol. 2012;13:89–99.
55. Schwarz TF, Huang LM, Medina DM, et al. Four-year follow-up of the immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine when administered to adolescent girls aged 10–14 years. J Adolesc Health. 2012;50:187–94.
56. Schwarz TF, Spaczynski M, Schneider A, et al. Persistence of immune response to HPV-16/18 AS04-adjuvanted cervical cancer vaccine in women aged 15–55 years. Hum Vaccines. 2011;7:958–65.
57. Romanowski B, Schwarz TF, Ferguson LM, et al. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: results from a randomized study. Hum Vaccines. 2011;7:1374–86.
58. Garcia-Sicilia J, Schwarz TF, Carmona A, et al. Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine coadministered with combined diphtheria–tetanus–acellular pertussis-inactivated poliovirus vaccine to girls and young women. J Adolesc Health. 2010;46:142–51.

59. Pedersen C, Breindahl M, Aggarwal N, et al. Randomized trial: immunogenicity and safety of coadministered human papillomavirus-16/18 AS04-adjuvanted vaccine and combined hepatitis A and B vaccine in girls. J Adolesc Health. 2012;50:38–46.
60. Schmeink CE, Bekkers RLM, Josefsson A, et al. Co-administration of human papillomavirus-16/18 AS04-adjuvanted vaccine with hepatitis B vaccine: randomized study in healthy girls. Vaccine. 2011;29:9276–83.
61. Wheeler CM, Harvey BM, Pichichero ME, et al. Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted vaccine coadministered with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine and/or meningococcal conjugate vaccine to healthy girls 11 to 18 years of age: results from a randomized open trial. Pediatr Infect Dis J. 2011;30:e225–34.
62. Verstraeten T, Descamps D, David MP, et al. Analysis of adverse events of potential autoimmune aetiology in a large integrated safety database of AS04 adjuvanted vaccines. Vaccine. 2008;26:6630–8.
63. Rambout L, Hopkins L, Hutton B, et al. Prophylactic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. CMAJ Can Med Assoc J. 2007;177:469–79.
64. Koutsky L, Ault K, Wheeler CM, et al. A controlled trial of a human papillomavirus type 16 vaccine. N Engl J Med. 2002;347:1645–51.
65. Lu B, Kumar A, Castellsague X, et al. Efficacy and safety of prophylactic vaccines against cervical HPV infection and diseases among women: a systematic review & meta-analysis. BMC Infect Dis. 2011;11:1–16.
66. Brown DR, Kjaer SK, Sigurdsson K, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16–26 years. J Infect Dis. 2009;199:926–35.
67. Wheeler CM, Kjaer SK, Sigurdsson K, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in sexually active women aged 16–26 years. J Infect Dis. 2009;199:936–44.
68. Mao C, Koutsky LA, Ault KA, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. Obstet Gynecol. 2006;107:18–27.
69. Einstein MH, Baron M, Levin MJ, et al. Comparison of the immunogenicity and safety of Cervarix (TM) and Gardasil (R) human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18–45 years. Hum Vaccines. 2009;5:705–19.
70. Einstein MH, Baron M, Levin MJ, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 vaccine and HPV-6/11/16/18 vaccine: follow-up from months 12–24 in a Phase III randomized study of healthy women aged 18–45 years. Hum Vaccines. 2011;7:1343–58.
71. Smith-McCune K. Quadrivalent HPV vaccine administered to women who became pregnant during trials did not appear to adversely affect pregnancy outcome; however, use during pregnancy is not recommended. Evid Based Med. 2010;15:80–1.
72. Dana A, Buchanan KM, Goss MA, et al. Pregnancy outcomes from the pregnancy registry of a human papillomavirus type 6/11/16/18 vaccine. Obstet Gynecol. 2009;114:1170–8.
73. Forinash AB, Yancey AM, Pitlick JM, et al. Safety of the HPV bivalent and quadrivalent vaccines during pregnancy. Ann Pharmacother. 2011;45:258–62.
74. Garland SM, Ault KA, Gall SA, et al. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized controlled trials. Obstet Gynecol. 2009;114:1179–88.
75. Merck Pregnancy Registry Program, Clinical Risk Management and Safety Surveillance. Fifth annual report on exposure during pregnancy from the Merck Pregnancy Registry for Quadrivalent Human Papillomavirus vaccine (Types 6, 11, 16, 18) recombinant vaccine [GARDASIL®/SILGARD™]. Coverage the period from first approval (June 1, 2006) through May 31, 2011. http://www.merckpregnacyregisteries.com (Accessed January, 2013).
76. Wacholder S, Chen BE, Wilcox A, et al. Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18: pooled analysis of two randomised controlled trials. BMJ. 2010;340:c712.
77. GalaxoSmithKline Pregnancy Registries. Cervarix™ Pregnancy Registry [online]. http://pregnancyregistry.gsk.com/cervarix.html (Accessed January, 2013).
78. Pasternak B, Svanström H, Mølgaard-Nielsen D, et al. Risk of adverse fetal outcomes following administration of a pandemic influenza A (H1N1) vaccine during pregnancy. JAMA. 2012;308:165–74.
79. Department of Health. Chapter 18a Human papillomaviurs (HPV). In: Salisbury D, Ramsay M, Noakes K, editors. The 'Green Book': immunisation against infectious disease. London: The Stationary Office; 2012.
80. Markowitz LE, Dunne EF, Saraiya M, et al. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2007;56:1–24.
81. Jacobson RM, Adegbenro A, Pankratz VS, et al. Adverse events and vaccination-the lack of power and predictability of infrequent events in pre-licensure study. Vaccine. 2001;19:2428–33.
82. Bonanni P, Cohet C, Kjaer SK, et al. A summary of the post-licensure surveillance initiatives for GARDASIL/SILGARD®. Vaccine. 2010;28:4719–30.
83. Medicines and Healthcare products Regulatory Agency (MHRA). YellowCard [online]. 2012. http://yellowcard.mhra.gov.uk/the-yellow-card-scheme/ (Accessed August, 2012).
84. Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), agencies of the U.S. Department of Health and Human Services. Vaccine Adverse Events Reporting System [online]. 2012. http://vaers.hhs.gov/index (Accessed August, 2012).
85. Iskander JK, Miller ER, Chen RT. Vaccine adverse event reporting system (VAERS). Pediatr Ann. 2004;33:599.
86. Public Health Agency of Canada. Adverse events following immunization reporting form [online]. 2012. http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php (Accessed 28th June).
87. Hawcutt DB, Mainie P, Riordan A, et al. Reported paediatric adverse drug reactions in the UK 2000–2009. Br J Clin Pharmacol. 2012;73:437–46.
88. Lindquist M. VigiBase, the WHO Global ICSR database system: basic facts. Drug Inf J. 2008;42:409–19.
89. Huang WT, Huang WI, Huang YW, et al. The reporting completeness of a passive safety surveillance system for pandemic (H1N1) 2009 vaccines: a capture–recapture analysis. Vaccine. 2012;30:2168–72.
90. Centre for Disease Control. Withdrawal of rotavirus vaccine recommendation. MMWR Wkly Rep. 1999;48:1007.
91. Collet JP, MacDonald N, Cashman N, et al. Monitoring signals for vaccine safety: the assessment of individual adverse event reports by an expert advisory committee. Bull World Health Organ. 2000;78:178–85.
92. Kliewer EV, Demers AA, Brisson M, et al. The Manitoba human papillomavirus vaccine surveillance and evaluation system. Health Rep. 2010;21:37–42.

93. Australian Government Department of Health and Ageing TGA. Human papillomavirus vaccine (Gardasil) advice from the therapeutic drug administration [online]. 2010. http://www.tga.gov.au/safety/alerts-medicine-gardasil-070624.htm (Accessed 27th June).
94. Slade BA, Leidel L, Vellozzi C, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA J Am Med Assoc. 2009;302:750–7.
95. van 't Klooster TM, Kemmeren JM, Vermeer-de Bondt PE, et al. Human papillomavirus vaccination catch-up campaign in 2009 for girls born in 1993 to 1996 in the Netherlands: results of the post-marketing safety surveillance. 2011.
96. The Medicines and Healthcare products Regulatory Agency (MHRA). Cervarix (HPV vaccine): update on UK safety covering the first two years of the HPV immunisation programme. 2010.
97. Brotherton JML, Gold MS, Kemp AS, et al. Anaphylaxis following quadrivalent human papillomavirus vaccination. Can Med Assoc J. 2008;179:525–33.
98. Kang LW, Crawford N, Tang MLK, et al. Hypersensitivity reactions to human papillomavirus vaccine in Australian schoolgirls: retrospective cohort study. Br Med J. 2008;337:a2642.
99. Labadie J. Postlicensure safety evaluation of human papilloma virus vaccines. Int J Risk Saf Med. 2011;23:103–12.
100. Advisory Committee on Immunization Practices. Summary Report. Antlanta: Department of Health and Human Services, Centre for Disease Control and Prevention; 2011.
101. Centre for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP) Summary Report. Atlanta: Centre for Disease Control and Prevention; 2011.
102. NHS Choices. HPV vaccine in the clear [online]. 2009. http://www.nhs.uk/news/2009/09September/Pages/Cervical-cancer-vaccine-QA.aspx (Accessed August, 2012).
103. Larson HJ, Brocard P, Garnett G. The India HPV-vaccine suspension. Lancet. 2010;376:572–3.
104. Pandhi D, Sonthalia S. Human papilloma virus vaccines: current scenario. Indian J Sex Transm Dis. 2011;32:75.
105. Institute of Medicine of the National A. Adverse events: evidence and causality. Washington, D.C.: The National Academies Press; 2011.
106. Richards S, Chalkiadis G, Lakshman R, et al. Complex regional pain syndrome following immunisation. Arch Dis Childhood. 2012;97:913–5.
107. Ojaimi S, Buttery JP, Korman TM. Quadrivalent human papillomavirus recombinant vaccine associated lipoatrophy. Vaccine. 2009;27:4876–8.
108. Siegrist CA, Lewis EM, Eskola J, et al. Human papilloma virus immunization in adolescent and young adults: a cohort study to illustrate what events might be mistaken for adverse reactions. Pediatr Infect Dis J. 2007;26:979–84.
109. Sutton I, Lahoria R, Tan I, et al. CNS demyelination and quadrivalent HPV vaccination. Multiple Scler. 2009;15:116–9.
110. Cooper Robbins SC, Bernard D, McCaffery K, et al. "I just signed": Factors influencing decision-making for school-based HPV vaccination of adolescent girls. Health Psychol. 2010;29:618–25.
111. LaRussa PS, Edwards KM, Dekker CL, et al. Understanding the role of human variation in vaccine adverse events: the Clinical Immunization Safety Assessment Network. Pediatrics. 2011;127:S65–73.
112. Wood NJ. The role of the Immunisation Adverse Events Clinic at The Children's Hospital at Westmead. N S W Public Health Bull. 2010;21:234–6.
113. Singh Y, Shah A, Singh M, et al. Human papilloma virus vaccination in Nepal: an initial experience in Nepal. Asian Pac J Cancer Prev. 2010;11:615–7.
114. Gasparini R, Bonanni P, Levi M, et al. Safety and tolerability of bivalent HPV vaccine: an Italian post-licensure study. Hum Vaccines. 2011;7(Suppl):136–46.
115. Naleway AL, Gold R, Drew L, et al. Reported adverse events in young women following quadrivalent human papillomavirus vaccination. J Women's Health. 2012;21:425–32.
116. Erlewyn-Lajeunesse M, Hunt LP, Heath PT, et al. Anaphylaxis as an adverse event following immunisation in the UK and Ireland. Arch Dis Childhood. 2012;97:487–90.
117. Velentgas P, Amato AA, Bohn RL, et al. Risk of Guillain–Barré syndrome after meningococcal conjugate vaccination. Pharmacoepidemiol Drug Saf. 2012;21:1350–8.
118. O'Leary ST, Glanz JM, McClure DL, et al. The risk of immune thrombocytopenic purpura after vaccination in children and adolescents. Pediatrics. 2012;129:248–55.
119. Chao C, Klein NP, Velicer CM, et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med. 2012;271:193–203.
120. Gee J, Naleway A, Shui I, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine. 2011;29:8279–84.
121. Yih WK, Kulldorff M, Fireman BH, et al. Active surveillance for adverse events: the experience of the Vaccine Safety Datalink Project. Pediatrics. 2011;127:S54–64.
122. Klein NP, Hansen J, Chao C, et al. Safety of quadrivalent human papillomavirus vaccine administered routinely to females. Arch Pediatr Adolesc Med. 2012;166:1140–8.
123. Tricotel A. Human papillomavirus vaccine and autoimmune disorders: a cohort study of 5.8 millions of adolescents and young women. Two years follow-up results. Fundam Clin Pharmacol. 2011;25:1.
124. Siegrist CA. Autoimmune diseases after adolescent or adult immunization: What should we expect? Can Med Assoc J. 2007;177:1352–4.
125. Callréus T, Svanström H, Nielsen NM, et al. Human papillomavirus immunisation of adolescent girls and anticipated reporting of immune-mediated adverse events. Vaccine. 2009;27:2954–8.
126. Van 't Klooster TM, Kemmeren JM, Van Der Maas NAT, et al. Reported adverse events in girls aged 13–16 years after vaccination with the human papillomavirus (HPV) 16/18 vaccine in the Netherlands. Vaccine. 2011;29:4601–7.
127. Crawford NW, Clotheir HJ, Elia S, et al. Syncope and seizures following human papillomavirus vaccination: a retrospective case series. Med J Aust. 2011;194:16–8.
128. Centre for Disease Control. General Recommendations on Immunization - Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2011;60:1–60.
129. Centre for Disease Control. Syncope after vaccination—United states, January 2005–July 2007. MMWR. 2008;57:457–60.
130. Centre for Disease Control. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). MMWR. 2010;59:626–9.
131. Souayah N, Michas-Martin P, Nasar A, et al. Guillain–Barré syndrome after Gardasil vaccination: data from vaccine adverse event reporting system 2006–2009. Vaccine. 2011;29:886–9.
132. World Health Organisation. Global Advisory Committee on Vaccine Safety, 17–18 December 2008. Wkly Epidemiol Rec (WER). 2009;5:37–40.
133. European Centre for Disease Prevention and Control (ECDC). Introduction of HPV vaccines in European Union countries—an update. Stolkholm: ECDC; 2012.

134. World Health Organisation. Global Advisory Committee on Vaccine Safety, 12–13 June 2007. Wkly Epidemiol Rec (WER). 2007:245–60.
135. Markowitz LE, Hariri S, Unger ER, et al. Post-licensure monitoring of HPV vaccine in the United States. Vaccine. 2010;28:4731–7.
136. Gold MS, McIntyre P. Human papillomavirus vaccine safety in Australia: experience to date and issues for surveillance. Sexual Health. 2010;7:320–4.
137. Mahajan D, Campbell-Lloyd S, Cook J, et al. NSW annual report describing adverse events following immunisation, 2010. N S W Public Health Bull. 2011;22:196–208.
138. Mahajan D, Reid S, Cook J, et al. NSW annual report describing adverse events following immunisation, 2011. N S W Public Health Bull. 2013;23:187–200.
139. Studdiford J, Lamb K, Norvath K, et al. Development of unilateral cervical and supraclavicular lymphadenopathy after human papillomavirus vaccination. Pharmocotherapy. 2008;28:1194–7.
140. Debeer P, De Munter P, Bruyninckx F, et al. Brachial plexus neuritis following HPV vaccination. Vaccine. 2008;26:4417–9.
141. Marsee DK, Williams JM, Velazquez EF. Aluminum granuloma after administration of the quadrivalent human papillomavirus vaccine. Report of a case. Am J Dermatopathol. 2008;30:622–4.
142. Das A, Chang D, Biankin A, et al. Pancreatitis following human papillomavirus vaccination. Med J Aust. 2008;189:178.
143. Schaffer V, Wimmer S, Rotaru I, et al. HPV vaccine: a cornerstone of female health a possible cause of ADEM? J Neurol. 2008;255:1818–20.
144. Wildemann B, Jarius S, Hartmann M, et al. Acute disseminated encephalomyelitis following vaccination against human papillomavirus. Neurology. 2009;72:2132–3.
145. DiMario FJ Jr, Hajjar M, Ciesielski T. A 16 year old girl with bilateral visual loss and left hemiparesis following an immunisation against human papillomavirus. J Child Neurol. 2010;25:321–7.
146. Wehbe E. A catastrophic failure. Am J Med. 2011;124:e7–9.
147. Bomprezzi R. Acute disseminated encephalomyelitis following vaccination against human papillomavirus. Neurology. 2010;72:2132–3.
148. Chang J, Campagnolo D, Vollmer TL, et al. Demyelinating disease and polyvalent human papilloma virus vaccination. J Neurol Neurosurg Psychiatry. 2011;82:1296–8.
149. Blitshteyn S. Postural tachycardia syndrome after vaccination with Gardasil. Eur J Neurol. 2010;17:e52.
150. Khalifa Y, Monahan P, Acharya N. Ampiginous choroiditis following quadrivalent human papilloma virus vaccine. Br J Ophthalmol. 2010;94:137–9.
151. McCarthy JE, Filiano J. Opsoclonus myoclonus after human papilloma virus vaccine in a pediatric patient. Parkinson Relat Disord. 2009;15:792–4.
152. Tuccori M, Pisani C, Bachini L, et al. Telogen effluvium following bivalent human papillomavirus vaccine administration: a report of two cases. Dermatology. 2012;224:212–4.
153. Rossi M. Bilateral papilledema following human papillomavirus vaccination. J Med Cases. 2011;2:222–4.
154. Pugnet G, Ysebaert L, Bagheri H, et al. Immune thrombocytopenic purpura following human papillomavirus vaccination. Vaccine. 2009;27:3690.
155. Soldevilla H, Briones S, Navarra S. Systemic lupus erythematosus following HPV immunization or infection? Lupus. 2012;21:158–61.
156. van't Klooster T, Kemmeren J, van der Maas N, et al. Reported adverse events in girls aged 13–16 years after vaccination with the human papillomavirus (HPV)-16/18 vaccine in the Netherlands. Vaccine. 2011;29:4601–7.