

REVIEW

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## Quadrivalent HPV vaccine safety review and safety monitoring plans for nine-valent HPV vaccine in the United States

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### ABSTRACT

Quadrivalent human papillomavirus (4vHPV) vaccine was licensed for use in the United States in 2006 and through 2015 was the predominate HPV vaccine used. With the exception of syncope, a known preventable adverse event after any injected vaccination, both pre-licensure and post-licensure 4vHPV safety data have been reassuring with no confirmed safety signals identified. Nine-valent HPV vaccine (9vHPV) was licensed in 2014. This review includes post-licensure 4vHPV safety findings published to date that have informed the US vaccination program; these data will inform US safety monitoring and evaluation for 9vHPV.

### ARTICLE HISTORY

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### Background

Human papillomavirus (HPV) vaccines are a powerful public health prevention tool for reducing the burden of cervical cancer and other HPV-related diseases worldwide. Three HPV vaccines that protect against HPV infection are available in the United States (US): bivalent HPV vaccine (Cervarix<sup>®</sup> [2vHPV] GlaxoSmithKline Biologicals), quadrivalent HPV vaccine (Gardasil<sup>®</sup> [4vHPV], Merck & Co. Inc.), and 9-valent HPV vaccine (Gardasil-9<sup>®</sup> [9vHPV] Merck & Co. Inc.). All three vaccines protect against HPV types 16 and 18, types which cause 70% of cervical cancers worldwide.<sup>1,2</sup> The 4vHPV and 9vHPV also protect against HPV types 6 and 11, types that cause more than 90% of genital warts. The 9vHPV targets five additional cancer-causing HPV types: HPV 31, 33, 45, 52, and 58. The Food and Drug Administration (FDA) licensed 4vHPV for females age 9–26 years in 2006, and for males in the same age group in 2009. FDA licensed 2vHPV in females in 2009 and 9vHPV for females and males at the end of 2014.<sup>2</sup>

Since 2006, the Advisory Committee on Immunization Practices (ACIP) has recommended routine vaccination of girls at age 11 or 12 and through age 26 for those not vaccinated. In 2011, routine vaccination of males was included in the immunization schedule. After licensure of 2vHPV in females and 9vHPV in females and males, ACIP updated recommendations to include these vaccines. Currently, ACIP recommends routine vaccination at age 11–12 years; vaccination can be started at age 9 years. HPV vaccination is also recommended for females aged 13–26 years and for males aged 13–21 years, if not previously vaccinated. In addition, vaccination is recommended for previously unvaccinated males age 22–26 years who are immunocompromised, test positive for human immunodeficiency virus (HIV), or have sex with men.

Safety of each HPV vaccine was studied extensively in pre-licensure clinical trials. 18,083 males and females were included in the 4vHPV clinical trials, 23,952 females for 2vHPV, and 23,081 subjects for 9vHPV, all with favorable safety findings.<sup>3–5</sup> Since the licensure of 4vHPV and 2vHPV, substantial observational post-licensure safety data have accumulated.<sup>6–9</sup> With the exception of syncope, a known preventable adverse event after any injectable vaccination, both pre-licensure and post-licensure HPV vaccine safety data to date have been reassuring with no confirmed safety signals (i.e. higher-than-expected numbers of adverse outcomes) identified. Despite the availability of these data, vaccine safety concerns have persisted and are reported by parents as one of the top 5 reasons for not initiating the HPV vaccination series.<sup>10,11</sup>

Although vaccine safety is rigorously assessed during pre-licensure clinical trials, sample sizes are not adequate to detect rare events, long term follow up for adverse events is not conducted, and populations are not always heterogeneous.<sup>12</sup> Post-licensure evaluation can determine if there are rare events that were not detected in pre-licensure trials. In the United States, post-licensure vaccine safety monitoring and evaluation plays an important role in supporting vaccination programs. The safety of HPV vaccines is monitored through manufacturer and government sponsored post-licensure studies.

In the United States, 4vHPV represents 99% of all HPV vaccine doses distributed through 2015.<sup>13</sup> As of September 2015, approximately 80 million 4vHPV doses and 0.8 million 2vHPV doses had been distributed in the United States. Because of the greater use of 4vHPV in the United States, the objective of this paper is to review post-licensure 4vHPV safety data published to date as well as unpublished data from the Vaccine Adverse

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Event Reporting System (VAERS) that have informed the US vaccination program and that will assist in planning for US safety monitoring and evaluation of 9vHPV. First, we review studies of the overall safety of 4vHPV and then focus on evaluation of specific conditions and populations (Table 1). The types of evaluations include safety reviews, summaries from VAERS, the US spontaneous reporting system, and large population-based studies from the United States and elsewhere. For special populations, we included studies from the manufacturer pregnancy registry as well as clinical trials in HIV-infected persons. We also present 9vHPV vaccine safety monitoring plans in the United States.

### General safety of 4vHPV

The general safety of 4vHPV has been described in multiple review papers, which have concluded that 4vHPV has a favorable safety profile.<sup>7,9</sup> These published safety reviews have included summaries of pre-licensure clinical trials as well as post-licensure experience involving surveillance, studies, case reports, and case series.

In 2009, the first summary of HPV vaccine safety data from the Vaccine Adverse Event Reporting System (VAERS) was published for 4vHPV.<sup>14</sup> This 2.5 year safety surveillance summary described US post-licensure adverse event reports from this spontaneous reporting system from June 1, 2006 through December 31, 2008. During the surveillance period, more than 23 million 4vHPV doses were distributed. There were a total 12,424 reports of which the majority were considered non-serious with syncope, dizziness, nausea, and headache being the most frequently reported symptoms. Overall, 6.2% were considered serious, which are reports defined as an event resulting in death, life-threatening illness, hospitalization, prolongation of existing hospitalizations, persistent or significant disability, a congenital anomaly or birth defect. As part of this VAERS surveillance summary, specific adverse events reported were assessed including injection site reactions, syncope, headache, hypersensitivity, Guillain-Barré Syndrome (GBS), transverse myelitis, motor neuron disease, venous thromboembolism (VTE), pregnancy, and death. This publication reported that the safety profile of 4vHPV was largely consistent with pre-licensure data, however, disproportional reporting was found for syncope and VTE. These were further investigated in other focused evaluations, discussed below.

Updated VAERS summaries have been published in 2013 and 2014.<sup>15,16</sup> In both reports, the data in VAERS identified no new safety concerns. CDC posts updated 4vHPV VAERS summaries on the CDC website regularly, and provides VAERS data online for analysis.<sup>17,18</sup>

In 2011, CDC's Vaccine Safety Datalink (VSD) published the first data from a large population-based post-licensure active surveillance project in the United States to evaluate the safety of multiple pre-specified events (outcomes) following 4vHPV among females aged 9–26 years.<sup>19</sup> As one of the main hypothesis testing vaccine safety systems in the United States, the VSD selected nine pre-specified outcomes based on the general safety data from pre-licensure clinical trials and reports to VAERS. They were clinically well defined with relatively acute onset, serious enough to result in a medical visit, and

represent a potentially biologically plausible association with vaccination. The pre-specified adverse outcomes identified by ICD-9 coded data were monitored weekly to detect associations with 4vHPV exposure and included: GBS, stroke, VTE, appendicitis, seizures, syncope, allergic reactions, and anaphylaxis. 600,558 4vHPV doses were administered during the surveillance period from August 2006 through October 2009. No statistically significant increased risk was found for any of the outcomes monitored. A non-statistically significant relative risk (1.98) for VTE following 4vHPV vaccination was detected among females age 9–17 years. Medical record review of the eight vaccinated possible VTE cases in this age group confirmed five cases. These confirmed cases had at least one known risk factor for VTE: hormonal contraceptive use, coagulation disorders, smoking, obesity, or prolonged hospitalization. The study concluded that additional evaluation was needed to assess the relationship between 4vHPV and VTE. For the outcome of anaphylaxis, because of the lack of specificity of the selected ICD-9 codes, medical record review was conducted for all identified anaphylaxis cases to calculate a confirmed incidence rate following 4vHPV. One case was confirmed; the calculated rate of anaphylaxis following 4vHPV in this study was 1.7 cases per million doses (95% CI: 0.04, 9.3). This rate of anaphylaxis following 4vHPV is similar to the expected rate of anaphylaxis following any vaccine (1.31 cases per million doses; 95% CI: 0.90–1.84).<sup>20</sup>

Because power to detect a true risk of GBS was limited, the VSD continued surveillance of GBS following 4vHPV until approximately 1.5 million doses were administered in the VSD population.<sup>13</sup> After medical record abstraction of the 2 cases identified in the electronic health plan data, VSD confirmed 0 cases of GBS, indicating that if there is an increased risk of GBS associated with HPV, it is likely to amount to less than 1.37 excess case per million vaccinated among 9–26 year olds.

As part of the post-licensure commitment to FDA, the manufacturer conducted a general safety assessment of 4vHPV routinely administered to females aged 9–26 years in a large, well-defined population.<sup>21</sup> This retrospective observational cohort study included 189,629 females who received at least one dose of 4vHPV as part of their routine clinical care at two large US health care delivery systems. A total of 346,972 doses were administered among the 189,629 females enrolled in the health plans in this study. ICD-9 coded diagnoses were identified using health plan electronic medical data from post-vaccination emergency department and hospitalization visits. Multiple analyses were conducted by dose with post-vaccination risk intervals of day 0, days 1–14, and days 1–60 among those who received at least one vaccine dose. Medical records were reviewed for events with elevated odds ratios identified from the electronic data. This study found an association of 4vHPV with same-day syncope and with skin infections in the two weeks after vaccination. After medical record review, some of the skin infections may have been local injection site reactions; although the medical records contained insufficient detail to exclude acute infections. Overall, females who received 4vHPV had increased health care utilization for skin conditions following vaccination. No other safety signals following 4vHPV were identified.



**Table 1.** Post-licensure published quadrivalent human papillomavirus vaccine (4vHPV) safety studies.

System or review (country)	Year of Publication	Number of doses evaluated	Type of concern addressed	Description	Methods	Findings
VAERS (US) <sup>a</sup>	2009	N/A	General safety	Summary of 12,424 VAERS reports following 4vHPV between 2006–2008	Spontaneous reporting; data mining for disproportional reporting	Disproportional reporting of syncope and VTE
Vaccine Safety Datalink (US) <sup>b</sup>	2011	600,558	General safety	Large database used for active surveillance and research; safety assessment of 9 pre-specified health outcomes among females vaccine recipients aged 9–26 years	Cohort design with weekly sequential analyses of electronic medical data	No statistically significant increase in risk for the outcomes monitored; non-significant elevated risk detected for VTE
Institute of Medicine review (US) <sup>c</sup>	2011	N/A	Review of safety data	Review of available 4vHPV safety data	Review of published studies, case reports, and surveillance systems	No evidence to support association among 12 outcomes; anaphylaxis causally associated with 4vHPV; syncope associated with all injectables
Post-marketing commitment to FDA (US) <sup>d</sup>	2012	346,972	General safety, VTE, neurologic, death	General assessment of safety following routine administration of 4vHPV at two large managed care organizations	Self-controlled risk interval design supplemented with medical record review	4vHPV associated with syncope on the day of vaccination and skin infections in the two weeks after vaccination; no other vaccine safety signals detected
Post-marketing commitment to FDA (US) <sup>e</sup>	2012	346,972	Autoimmune	Assessment of 16 pre-specified autoimmune conditions following routine use of 4vHPV at two large managed care organizations	Retrospective cohort using electronic medical data, supplemented with medical record review	No confirmed safety signals for monitored conditions
VAERS (US) <sup>f</sup>	2013	N/A	General safety	Review of 21,194 VAERS reports following 4vHPV between 2006–2013	Spontaneous reporting; data mining for disproportional reporting	No disproportional reporting observed; no new concerns
Register-based cohort study (Denmark and Sweden) <sup>g</sup>	2013	696,420	Autoimmune, Neurologic, VTE	Assessment of 23 different autoimmune, 5 neurologic conditions, and VTE following 4vHPV among females aged 10–17 years	Retrospective cohort using national patient registers	No consistent evidence of causal association between 4vHPV and the events monitored
VAERS (US) <sup>h</sup>	2014	N/A	General safety	Review of 25,176 VAERS reports following 4vHPV between 2006–2014	Spontaneous reporting; data mining for disproportional reporting	No disproportional reporting observed; no new concerns
Pharmacoepidemiologic General Research Extension (France) <sup>i</sup>	2014	N/A	Autoimmune	Assessment of 6 different autoimmune outcomes following 4vHPV among 211 cases and 875 controls aged 14–26 years	Case-control study with recruitment of cases and controls through registries	No increased risk for combined endpoint of six autoimmune disorders
Register-based cohort study (Denmark) <sup>j</sup>	2014	500,345	VTE	Assessment of VTE following 4vHPV among women aged 10–44 years	Self-controlled case series using national patient registers	No increased risk for VTE

Table 1. (Continued)

System or review (country)	Year of Publication	Number of doses evaluated	Type of concern addressed	Description	Methods	Findings
Register-based cohort study (Denmark and Sweden) <sup>k</sup>	2015	1,927,581	Autoimmune	Assessment of multiple sclerosis and other demyelinating diseases of the central nervous system among females aged 10–44 years	Cohort design using data linked to national registers	No association with the development of multiple sclerosis and other demyelinating diseases
Vaccine Safety Datalink (US) <sup>l</sup>	2015	1,240,000	VTE	Assessment of VTE among adolescents and young adults aged 9–26 years	Self-controlled case series; cases confirmed by medical record review	No increase risk for VTE
Sentinel System (US) <sup>m</sup>	2015	1,423,399	VTE	Assessment of VTE among females aged 9–26 years	Self-controlled risk interval design; cases confirmed by medical record review	No increased risk for VTE
VAERS (US) <sup>n</sup>	2015	N/A	Neurologic	Review of 21 CRPS-related VAERS reports following 4vHPV between 2006 and 2015	Spontaneous reporting; clinical review of CRPS cases	Lack of evidence to suggest an association; data suggest CRPS following HPV vaccine is rare
Post-marketing commitment to FDA (US) <sup>o</sup>	2015	N/A	Pregnancy	Review of 4,919 reports of pregnancy following 4vHPV between 2006–2012	Voluntary reporting to pregnancy registry	Data were reassuring with no elevated reporting of adverse pregnancy outcomes
VAERS (US) <sup>p</sup>	2015	N/A	Pregnancy	Review of 147 VAERS pregnancy reports following 4vHPV between 2006 and 2013	Spontaneous reporting; data mining for disproportional reporting	No unexpected patterns fetal adverse events after 4vHPV
Vaccine Safety Datalink (US) <sup>q</sup>	2016	1,355,535	Death	Evaluation of deaths among individuals aged 9–26 years	Case-centered method; medical record review	Rate of death was lower than the national expected rate of death in this population

Abbreviations

CRPS- Chronic Regional Pain Syndrome, FDA- Food and Drug Administration, HIV- Human immunodeficiency virus, 4vHPV- Quadrivalent Human Papillomavirus vaccine, VAERS- Vaccine Adverse Event Reporting System, VTE- Venous thromboembolism

Sources

- <sup>a</sup>Slade, B.A., et al., Post-licensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA*, 2009. 302(7): p. 750–757.
- <sup>b</sup>Ge, J., et al., Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. *Vaccine*, 2011. 29(46): p. 8279–8284.
- <sup>c</sup>Institute of Medicine. *Adverse Effects of Vaccines: Evidence and Causality*, 2011.
- <sup>d</sup>Klein, N.P., et al., Safety of quadrivalent human papillomavirus vaccine administered routinely to females. *Arch Pediatr Adolesc Med*, 2012. 166(12): p. 1140–8.
- <sup>e</sup>Chao, C., et al., Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. *J Intern Med*, 2012. 271(2): p. 193–203.
- <sup>f</sup>Stokley S, et al., Human Papillomavirus Vaccination Coverage Among Adolescent Girls, 2007–2012, and Postlicensure Vaccine Safety Monitoring, 2006–2013 — United States. *MMWR Recomm Rep*, 2013. 62(29): p. 591–595
- <sup>g</sup>Arnheim-Dahlstrom, L., et al., Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. *BMJ*, 2013. 347: p. f5906.
- <sup>h</sup>Stokley S, et al., Human papillomavirus vaccination coverage among adolescent girls, 2007–2012, and post-licensure vaccine safety monitoring, 2006–2013 — United States. *MMWR Recomm Rep*, 2014. 63(29): p. 620–4.
- <sup>i</sup>Grimaldi-Bensouda, L., et al., Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. *J Intern Med*, 2014. 275(4): p. 398–408.
- <sup>j</sup>Scheller, N.M., et al., Quadrivalent human papillomavirus vaccine and the risk of venous thromboembolism. *JAMA*, 2014. 312(2): p. 187–8.
- <sup>k</sup>Scheller, N.M., et al., Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. *JAMA*, 2015. 313(1): p. 54–61.
- <sup>l</sup>Haleway, A.L., et al., Absence of venous thromboembolism risk following quadrivalent human papillomavirus vaccination. *Vaccine Safety Datalink, 2008–2011*. *Vaccine*, 2016; 34(1): p. 167–71.
- <sup>m</sup>Yih, W.K., et al., Evaluation of the risk of venous thromboembolism after quadrivalent human papillomavirus vaccination among US females. *Vaccine*, 2016; 34(1): p. 172–8.
- <sup>n</sup>Weinbaum C, et al., HPV Vaccination and Complex Regional Pain Syndrome: Lack of Evidence. *EBioMed*, 2015. 2(9): p. 1014–1015.
- <sup>o</sup>Goss, M.A., et al., Final report on exposure during pregnancy from a pregnancy registry for quadrivalent human papillomavirus vaccine. *Vaccine*, 2015. 33(29): p. 3422–8.
- <sup>p</sup>Moro, P.L., et al., Safety of quadrivalent human papillomavirus vaccine (Gardasil) in pregnancy: adverse events among non-manufacturer reports in the Vaccine Adverse Event Reporting System, 2006–2013. *Vaccine*, 2015. 33(4): p. 519–22.
- <sup>q</sup>McCarthy, N.L., et al., Lack of association between vaccination and death in individuals 9–26 years of age. *Pediatrics*, 2016; 137(3): p. 1–8.

In summary, to date, reviews of the general safety of 4vHPV have indicated a favorable safety profile. Extended studies of long-term safety up to 14 years following 4vHPV vaccination in different populations of males and females are being conducted by the manufacturer.<sup>9</sup>

### Specific conditions

In addition to studies of multiple health conditions among persons who received HPV vaccines, investigations of specific health conditions or groups of health conditions have been conducted in response to suggested associations or case reports.

### Autoimmune disease

Many autoimmune diseases manifest during the young adult years. There have been several case reports of autoimmune diseases following 4vHPV, however, such reports do not necessarily provide evidence of a causal association between vaccine and the adverse event.<sup>22-24</sup> Concerns of autoimmune disease following vaccination have been described and with the introduction of a new vaccine, particularly in adolescents, reports were anticipated.<sup>25-27</sup> In addition, an unmasking phenomenon may occur in which a healthcare visit for a vaccination may initiate a medical evaluation of signs and symptoms that later result in a diagnosis of a prevalent disease.<sup>28</sup>

As part of the post-marketing commitment to FDA, a large post-licensure study by the manufacturer was conducted at two large US health delivery systems to assess the risk of autoimmune disease following 4vHPV.<sup>29</sup> The study population included 189,629 women of all ages who received at least one dose of 4vHPV between August 2006 and March 2008; 99% of the women were age 9–26 years. In this study, three groups of pre-specified autoimmune conditions of interest were analyzed: rheumatologic/autoimmune disorders (including immune thrombocytopenia, autoimmune hemolytic anemia, systemic lupus erythematosus, rheumatoid arthritis, and juvenile rheumatoid arthritis), autoimmune endocrine conditions (including type 1 diabetes, Hashimoto's disease and Graves' disease), and autoimmune neurological/ophthalmic conditions (including multiple sclerosis (MS), acute disseminated encephalomyelitis, other demyelinating diseases of the central nervous system, vaccine associated demyelination, GBS, neuromyelitis optica, optic neuritis, and uveitis). Women were followed for up to 180 days after each 4vHPV dose using ICD-9 coded diagnoses, abnormal laboratory, or electronic medical record data to identify new-onset autoimmune conditions. A total of 719 potential new onset cases were identified and 347 were sampled for case review by clinical expert panel. Because of the large number of potential new-onset cases identified for SLE, RA, JRA, Hashimoto's and Graves' disease, a random sample of potential cases for these conditions was included for case review. For other autoimmune conditions, all eligible potential new-onset cases were reviewed by the clinical expert panel. No cluster of disease onset in relation to vaccination timing, dose sequence, or age for any autoimmune condition was observed. When compared to background rates, none of the observed incidence rates was found to be significantly increased except for Hashimoto's disease (incidence rate ratio (IRR) 1.29, 95% CI: 1.08–1.56). The

safety review committee interpreted this as unlikely to be a causal association. This was based on the lack of consistent evidence for a safety signal for autoimmune thyroid conditions in which disease onset was mostly randomly distributed in relation to the vaccination timing; there was no consistent elevation in incidence for autoimmune thyroid conditions in the vaccination cohort and several of the new onset autoimmune thyroid conditions were likely pre-existing at the time of vaccination. The study concluded that autoimmune conditions were unlikely to be caused by 4vHPV vaccine in routine clinical use.

Post-licensure safety investigations from other countries have also provided reassuring data on the lack of association between autoimmune disease and 4vHPV. In France, a case-control study using national patient registries was conducted to assess the association between 4vHPV and autoimmune diseases.<sup>30</sup> The study population was all female and included 211 cases and 875 controls aged 14–26 years. Autoimmune diseases investigated included idiopathic thrombocytopenia purpura (ITP), connective tissue disorders (undifferentiated connective tissue disorder, lupus erythematosus, rheumatoid arthritis/juvenile arthritis), central demyelination and MS, GBS, type 1 diabetes mellitus, and autoimmune thyroid disorders, including Graves' and Hashimoto's diseases. Using prescription records and data collected from telephone interviews, data were collected on 4vHPV vaccination and other potential risk factors for autoimmune diseases. Multivariate conditional logistic regression analyses found no association between 4vHPV and the studied autoimmune diseases.

A large population based study assessed the risk of autoimmune conditions after vaccination in Denmark and Sweden.<sup>31</sup> Using national health care registries, this cohort study included a total of 997,585 girls of whom 296,826 (29%) received a total of 696,420 4vHPV doses between October 1, 2006 and December 31, 2010. Twenty-three pre-defined autoimmune events were assessed, as identified from inpatient, outpatient, and emergency department visits. Because of a high probability of chance findings, only outcomes with at least five exposed cases during the outcomes specific pre-defined period of risk were included in the study analyses. Three signal strengthening criteria were employed before any significant result was determined to be a signal: 1) analysis based on 20 or more vaccine exposed cases (reliability); 2) a rate ratio of 3.0 or more (strength of association); and 3) significantly increased rate ratios in country specific analyses (consistency). Significant rate ratios were observed with Bechet's syndrome, Raynaud's disease, and type 1 diabetes; however, each of these outcomes fulfilled only one of the three predefined signal strengthening criteria. Upon further assessment of these three outcomes, it was concluded that there was no consistent evidence of causal associations. This study found no evidence to support associations between exposure to 4vHPV and autoimmune conditions.

In another study conducted in Denmark and Sweden using national registries, a cohort of 3,983,824 females aged 10–44 years were followed from 2006 to 2013 to assess the association between 4vHPV and MS and other demyelinating diseases.<sup>32</sup> 789,082 women received a total of 1,927,581 4vHPV vaccine doses. In this cohort study, IRRs were estimated using Poisson regression comparing rate of events in the two year risk periods following vaccination and in unvaccinated time

periods; no association was found between MS or other demyelinating disease and 4vHPV vaccine.

Through the media, reports of primary ovarian insufficiency (POI) have been publicized after receipt of 4vHPV.<sup>33,34</sup> POI has been associated with myriad etiologies, including autoimmune, genetic, enzymatic, infectious, inflammatory, and idiopathic causes.<sup>35-37</sup> A review of VAERS data from June 2006 to September 2015, when approximately 80 million doses had been distributed in the United States, identified nine reports of POI following receipt of 4vHPV.<sup>17</sup> An additional ten VAERS reports of related condition “ovarian disorder” or “ovarian failure” were received following 4vHPV. Among these reports, there were no consistent patterns, and the review produced no evidence to suggest a causal association between 4vHPV and POI. The VSD is conducting a study to address this issue.<sup>13</sup>

### **Venous thromboembolism (VTE)**

Because of the inconclusive findings regarding a potential association between 4vHPV and VTE identified from VAERS and VSD monitoring, as noted above, additional studies were conducted. These include two large population based studies using national registry data from Denmark and Sweden and two large US government-sponsored studies.

In the previously mentioned study using national registries in Denmark and Sweden, 696,420 doses of 4vHPV administered among 296,826 females aged 10–17 years between October 2006 and December 2010 were evaluated to determine if 4vHPV was associated with VTE.<sup>31</sup> The risk window for VTE in this retrospective cohort study was 90 days after vaccine exposure. VTE was identified using ICD-10 diagnostic codes. No significant association was identified for VTE; the rate ratio between 4vHPV exposure and VTE was 0.86 (95% CI: 0.55–1.36) in females vaccinated with 4vHPV as compared to those unvaccinated.

A second large study using Danish national registers included 1,613,798 women aged 10–44 years between October 2006 and July 2013.<sup>38</sup> 500,345 (31%) females received 4vHPV. A total of 4,375 incident cases of VTE were identified using ICD-10 diagnosis codes; 889 had been vaccinated during the study period. Using a self-controlled case series method, which eliminates confounding by time-independent factors, no association was observed between 4vHPV and VTE during the 42 days following vaccination (overall IRR 0.77; 95% CI: 0.53–1.11). No association was found in sub-analyses stratifying by age, anticoagulant use, or oral contraceptive use.

A follow-up study was conducted in the VSD to investigate the non-significant elevated relative risk of VTE following 4vHPV among females detected in its previous study.<sup>19,39</sup> This study included over 1.24 million doses of 4vHPV administered to 650,737 participants between January 2008 and December 2011. The study population included 313 adolescents and young adults aged 9–26 diagnosed with VTE who received at least one 4vHPV dose. Medical record review was utilized to confirm presumptive VTE diagnoses. Among the 161 confirmed cases, 97% had at least one known risk factor for VTE including hormonal contraceptive use, obesity, and hypercoagulability. Using self-controlled case series methodology, the risk of VTE varied from 1.47 (95% CI: 0.47–4.64) in the 1–

7 days following 4vHPV exposure to 0.92 (95% CI: 0.54–1.57) in the 1–60 days following vaccination. No elevated risk for VTE following 4vHPV was observed in this study. The FDA’s Sentinel System, a large national electronic system to monitor FDA-approved products using claims-based insurance data, evaluated the risk of VTE in more than 650,000 females aged 9–26 years.<sup>40</sup> The study included 1,423,399 doses of 4vHPV administered, of which 46% were first doses. ICD-9 codes consistent with first-ever VTE were confirmed by medical record review. Risk factors for VTE cases were collected. Using self-controlled risk interval analyses, which controls for time-invariant confounding, and adjustment for time-varying VTE risk from contraceptive use, the study found no evidence of an increased risk of VTE 1–7 days or 1–28 days following 4vHPV vaccination.

VTE was also evaluated as an outcome of interest in the FDA post-marketing manufacturer commitment of the general safety of 4vHPV.<sup>21</sup> No association between 4vHPV and VTE was found in that study.

### **Neurologic disease**

Neurologic events that have occurred following 4vHPV have resulted in decreased acceptance and/or the disruption of immunization programs.<sup>41</sup> For example, in October 2009, Spain’s vaccination program was suspended for two months after two cases of status epilepticus were found to be temporally related to receipt of 4vHPV.<sup>42</sup> In 2013, Japan suspended proactive recommendations for HPV vaccination due to concerns from the public about adverse events related to chronic pain and numbness of the extremities.<sup>41,43</sup>

The reports in Japan suggested potential cases of complex regional pain syndrome (CRPS), a clinical syndrome that is characterized by persistent pain in an extremity disproportionate to the inciting event and at least one sign of autonomic dysfunction in the affected limb.<sup>44</sup> While the pathogenesis of CRPS is poorly understood, it has been suggested that reported CRPS following vaccination may be a result of minor trauma from injection. In a review of VAERS reports, between 2006 and July 23, 2015, there were 21 reports of CRPS related reports following 4vHPV (MedDRA search terms: “complex regional pain syndrome” and “mononeuropathy multiplex”).<sup>45</sup> With over 80 million doses of 4vHPV distributed in the United States through September 2015, the findings from VAERS indicate that CRPS is rare following HPV vaccination.

Orthostatic intolerance and postural tachycardia syndrome (POTS) have been reported following HPV vaccine.<sup>46,47</sup> POTS is a subset of orthostatic intolerance that is associated with the presence of excessive tachycardia on standing.<sup>48</sup> The etiology of POTS is unknown but is likely to be heterogeneous, with the syndrome associated with deconditioning, recent viral illness, chronic fatigue syndrome and a limited or restricted autonomic neuropathy.<sup>49</sup> POTS is more common in females, with a 5:1 ratio to males.<sup>47</sup> In November 2015, the European Medicine’s Agency announced its Pharmacovigilance Risk Assessment Committee completed a detailed review of available data surrounding CRPS and POTS in young women following HPV vaccines. The review concluded that the evidence does not

support a causal link between HPV vaccine and these two syndromes.<sup>50</sup>

Neurological outcomes were also assessed in the previously mentioned large study using national registry data in Denmark and Sweden.<sup>31</sup> Among this cohort of 997,585 girls aged 10–17 years, a retrospective cohort study assessed the relationship between 4vHPV and 12 neurological outcomes. Five of these outcomes fulfilled the criterion for further analysis due to  $\geq$  five cases within the risk period. These included Bell's palsy, epilepsy, narcolepsy, optic neuritis, and paralysis. Additional analyses found rate ratios not significantly increased for any of the five neurological outcomes. Rate ratios were significantly decreased for epilepsy and paralysis.

## Death

Isolated reports of death following HPV have been highly publicized in the media. For example, in 2009, a young girl died on the same day as receipt of HPV vaccine, sparking national controversy. Further investigation determined the cause of death to be due to a large malignant chest tumor of unknown origin.<sup>51</sup> In 2014, a 12 year old died hours after receipt of 4vHPV.<sup>52</sup> The cause of death was ultimately determined to be due to an antihistamine overdose. Determining the cause of death for cases temporally associated with vaccination is critical to assess casual associations in order to decrease rumors and unfounded safety concerns about vaccination.

In VAERS, between June 2006 and September 2015, after 80 million vaccine doses had been distributed in the United States, there were 117 reports of death among persons who received 4vHPV.<sup>17</sup> Among these 117 reports of death, only 51 reports had a certificate of death, autopsy report, or other medical documentation of death available. The remaining 66 reports of death to VAERS were considered unverified meaning there was no accompanying information to confirm the death. Clinical review of these deaths found no pattern with respect to time after vaccination, vaccine dose number, combination of vaccines administered, or diagnosis at death that would suggest a causal association with 4vHPV.

The VSD conducted a study evaluating deaths occurring between January 2005 and December 2011 following immunizations, among individuals 9–26 years.<sup>53</sup> A case-centered method was utilized which used a vaccinated cohort only and adjusted for seasonal variation in mortality and vaccine administration. Medical records and coroners reports were reviewed to assess the causal relationship between death and vaccination. There were 13 deaths identified within 0–30 days after vaccination, of which 9 were due to external causes (accident, homicide, or suicide). Of the remaining four deaths, these were due to non-external causes. Two of these deaths were determined to be unrelated to vaccination and the other two did not have sufficient evidence to confirm or rule out a causal association. The rate of death following 4vHPV in this study was 11.7 deaths per 100,000 person-years and was significantly lower than the expected rate of death for all causes. The National Center for Health Statistics' published 2011 death rate for all causes most similar to this study's population among persons 15–24 years was 67.6 deaths per 100,000 persons.<sup>54</sup> This study

concluded that the risk of death was not increased during the 30 days following vaccination and no deaths were found to be causally associated with vaccination after review.

Death was also a pre-specified outcome evaluated with chart review in the general safety assessment conducted by Klein et al.<sup>21</sup> Among the 14 deaths that occurred after 346,972 4vHPV doses, none were found to have a relationship with vaccination.

## Subpopulations

### Pregnant women

4vHPV is not recommended for use in pregnant women.<sup>55</sup> There are no adequate or well-controlled 4vHPV safety studies in pregnant women. However, in the clinical trials, inadvertent vaccination shortly before or during pregnancy occurred in over 4,000 pregnancies.<sup>56</sup> Compared with 2,029 pregnancies in the placebo group, there were no significant differences in the proportions of 2,008 pregnancies in the vaccine group resulting in live birth, fetal loss, or spontaneous abortion. Among those infants born to women who received vaccine or placebo within 30 days of estimated onset of pregnancy in the pre-licensure trials, there were five congenital anomalies in the vaccine group (N= 128) and one in the placebo group (N=138). A clinical expert review panel determined the five congenital anomalies to be unrelated to the vaccine. In 2015, a published review of the safety profile of 4vHPV exposures from the 2006–2012 Merck pregnancy registry summarized 4,919 reports of 4vHPV exposure during pregnancy from June 1, 2006 through May 31, 2012.<sup>57</sup> Among those meeting eligibility criteria, 2,566 were prospective reports of pregnant women who received vaccine before the outcome of the pregnancy was known. There also were 376 retrospective reports received after the outcome of pregnancy was known. Among the 2,566 prospective reports, there were 1,752 reports with a known outcome, of which 87% were live births. Of the 1,527 neonates, 95% had no congenital anomalies. The overall rate of spontaneous abortion was calculated to be 6.7 per 100 pregnancies (95% CI: 5.5–8.2) and the prevalence of major birth defects was 2.4 per 100 live-born neonates (95% CI: 1.7–3.3). There were 12 fetal deaths (0.8 per 100 pregnancies; 95% CI: 0.4–1.4). The data from this pregnancy registry are reassuring with respect to the rate of spontaneous abortion, the rate of fetal death, and the overall rate of congenital anomalies. Spontaneous abortion rates were found to be lower than national rates, fetal death rates in this study were within the range of published rates, and the overall rate of congenital anomalies was comparable to the expected prevalence rate of major malformations at birth.

In a clinical review of non-manufacturer reports received in VAERS between June 2006 and December 2013, there were 147 reports of 4vHPV administered to pregnant women.<sup>58</sup> The most frequent pregnancy-related adverse event reported was spontaneous abortion (10.2%), followed by elective termination (4.1%). Maternal fever was reported in 2% and was the most frequently reported non-pregnancy related report. There were two reports of major birth defects and no maternal deaths reported. Similar to the findings from the manufacturer pregnancy registry results, this analysis found no unexpected patterns of fetal adverse events after 4vHPV. With regards to

reported maternal adverse events, no unexpected patterns were identified.

## HIV

4vHPV is recommended for HIV-infected persons in the targeted age groups for routine and catch-up vaccination and for unvaccinated males 22–26 years of age.<sup>55</sup> While studies among HIV infected persons were not conducted pre-licensure, six small post-licensure trials of immunogenicity and safety of 4vHPV have been reported. (Table 2) In one trial, 126 children aged 7–12 with HIV infection were randomly assigned to receive 4vHPV or placebo; participants were observed in clinic for 30 minutes post-vaccination and completed daily diary cards.<sup>59</sup> AEs were similar between treatment arms. In addition, the safety of 4vHPV in HIV-infected children was similar to that reported among HIV-uninfected children, 9–15 years of age. Through the AIDS Malignancy Consortium (<https://web.emmes.com/study/amc/public/>), a clinical trial was conducted in the United States to assess the safety and immunogenicity of 4vHPV of HIV infected men aged 18 or older.<sup>60</sup> 109 study participants who received at least one dose of 4vHPV were included in the safety analyses. Study monitoring included clinical assessments of vaccine related symptoms for the first 48 hours after vaccination, diary entries for 5 days after

vaccination and clinical assessments through 28 weeks post-vaccination. No severe adverse events related to vaccination were found, however, injection site reactions occurred in 18%, 17%, and 12% after the first, second, and third doses, respectively. Another multicenter clinical trial evaluated the safety of 4vHPV among 319 HIV-infected women aged 13–45 years.<sup>61</sup> Clinical assessments were made at each vaccination and at weeks 4, 12, and 28 and participants were also contacted 24–48 hours post-vaccination. There were no significant safety concerns identified in this study. Similar results were observed in another study evaluating 99 HIV-infected women age 16–23 years.<sup>62</sup> In this study, post-vaccination symptoms were collected through the 7 days after vaccination and vaccine report card or a telephone response system to record adverse events through first 7 days post-vaccination. 4vHPV was generally well tolerated, with the most common report being pain (26.3% of participants). Comparing safety in 46 HIV-infected and 46 HIV-uninfected males and females, an assessment using diary cards of local and systemic side effects during the 7 days after each 4vHPV dose found 4vHPV was well tolerated in both groups.<sup>63</sup> In a study comparing the safety of 4vHPV to 2vHPV among 92 HIV-infected men and women 18 years or older, no serious adverse events were detected in the 15 days post-vaccination and both vaccines were well tolerated with very few mild systemic reactions observed.<sup>64</sup>

**Table 2.** Post-licensure clinical trials of the safety of quadrivalent human papillomavirus vaccine (4vHPV) among HIV-infected persons.

Year of Publication	Description	Methods	Findings
2010 <sup>a</sup>	Assessment of safety of 4vHPV among 126 HIV-infected children 7–12 years	Randomized, placebo-controlled, double-blinded study; observation post-vaccination; diary cards and telephone response	Adverse events were similar between treatment arms
2010 <sup>b</sup>	Assessment of safety of 4vHPV among 112 HIV-infected men 18 years and older	Single arm, open label, multicenter clinical trial; clinical assessment post vaccination and at defined time points; diary card	No severe adverse events related to vaccination
2013 <sup>c</sup>	Assessment of safety of 4vHPV among 99 HIV-infected women 16–23 years	Open-label, multicenter clinical trial; clinical assessment post-vaccination and at defined time points; diary card and telephone response	4vHPV well tolerated; pain most common report
2014 <sup>d</sup>	Assessment of safety of 4vHPV among 319 HIV-infected women 13–45 years	International phase 2, open label, single-arm study with stratification by CD4+ cell count; clinical assessments post vaccination and at defined time points	No significant safety issues observed
2014 <sup>e</sup>	Assessment of safety of 4vHPV among 46 HIV-infected and 46 HIV-uninfected males and females aged 13–27 years	Non-randomized, open label clinical trial; observation post-vaccination; diary card	4vHPV safe and well tolerated among HIV-infected and HIV-uninfected participants
2014 <sup>f</sup>	Assessment of the safety of 4vHPV versus 2vHPV among 92 HIV-infected men and women	Randomized, double-blind, head-to-head clinical trial of 2vHPV and 4vHPV	No serious adverse events were detected; both vaccines were well tolerated with very few mild systemic reactions observed

Abbreviation: HIV- Human immunodeficiency virus; 2vHPV- bivalent human papillomavirus vaccine

Sources:

<sup>a</sup>Levin, M.J., et al., Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. *J Acquir Immune Defic Syndr*, 2010. 55(2): p. 197–204.

<sup>b</sup>Wilkin, T., et al., Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. *J Infect Dis*, 2010. 202(8): p. 1246–53.

<sup>c</sup>Kahn, J.A., et al., Immunogenicity and safety of the human papillomavirus 6, 11, 16, 18 vaccine in HIV-infected young women. *Clin Infect Dis*, 2013. 57(5): p. 735–44.

<sup>d</sup>Kojic, E.M., et al., Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. *Clin Infect Dis*, 2014. 59(1): p. 127–35.

<sup>e</sup>Giacomet V., et al., Safety and immunogenicity of a quadrivalent human papillomavirus vaccine in HIV-infected and HIV-negative adolescents and young adults. *Vaccine*, 2014; 32(43): p. 5657–61.

<sup>f</sup>Toft L., et al., Comparison of the immunogenicity and reactogenicity of Cervarix and Gardasil human papillomavirus vaccines in HIV-1 infected adults: a randomized, double-blind clinical trial. *J Infect Dis*. 2014; 209 (8): p. 1165–73.



## 9-Valent HPV vaccine

9-valent HPV vaccine (9vHPV) was recommended by ACIP in February 2015, as one of the three HPV vaccines for routine immunization for females and one of two for males. Like 4vHPV, 9vHPV is a virus-like particle (VLP) vaccine which uses the L-1 protein of the virus as the immunogen. The main difference between the two vaccines is the antigen content due to the additional HPV types targeted. Both vaccines contain the same adjuvant, however 4vHPV contains approximately 225mcg of aluminum while 9vHPV contains 500mcg of aluminum.<sup>3,5</sup> Pre-licensure safety data were evaluated in approximately 23,000 subjects from seven pre-licensure studies.<sup>5</sup> 9vHPV was well tolerated as most adverse events were injection site pain, swelling, and erythema that were mild to moderate intensity. The adverse event profile was similar to that of 4vHPV across age, gender, race, and ethnicity although there were more injection site reactions with 9vHPV compared with 4vHPV, including swelling (40.3% in the 9vHPV group compared with 29.1% in the 4vHPV group) and erythema (34.0% in the 9vHPV group compared with 25.8% in the 4vHPV group).<sup>2</sup> Among inadvertent pregnancies occurring during the clinical studies, the proportion of adverse outcomes observed was consistent with those observed in the general population. Sub-analyses conducted included pregnancies with an estimated onset within 30 days of vaccination, the proportion of pregnancies resulting in a spontaneous abortion occurred more frequently among those who received 9vHPV compared with 4vHPV (9vHPV group 27.4% (17/62) vs. 4vHPV group 12.7% (7/55)). The rates of spontaneous abortions observed in both groups were within the expected background rate of early loss in pregnancy.<sup>65</sup>

### 9vHPV vaccine safety monitoring in the United States

9vHPV is expected to have the same good safety profile as 4vHPV; however, it is important to continue vaccine safety monitoring for 9vHPV. This vaccine was introduced into the United States in early 2015 and will completely replace 4vHPV by the end of 2016. Ongoing vaccine safety monitoring for vaccines in use in the US population is conducted using several well established systems, including VAERS, the Clinical Immunization Safety Assessment (CISA) Network, VSD, and FDA's Sentinel System. Post-licensure safety evaluations are also conducted through FDA post-marketing commitments by the manufacturer.

VAERS is jointly operated by CDC and FDA and is the nation's frontline spontaneous reporting system to detect potential vaccine safety problems.<sup>66</sup> VAERS, including its limitations, has been well described.<sup>14,45,58,67</sup> Because of its limitations, determining causal associations between vaccines and adverse event is not possible using VAERS data alone. As a hypothesis generating system, VAERS identifies potential vaccine safety concerns that can be further studied in more robust data systems. Reports following 9vHPV will be monitored using VAERS automated data. Clinical reviews of any deaths that are reported to VAERS as well as other pre-specified adverse events will be conducted. FDA will review all serious adverse events and conduct empirical Bayesian data mining to identify any disproportional reporting within the VAERS data. For any complex cases that are reported to VAERS, CDC's

CISA project will provide clinical consultation and determine vaccine association.

The VSD is a collaboration between CDC and 9 US integrated healthcare delivery systems with an annual population of 9.2 million members and has proven to be a highly effective tool for evaluating and monitoring vaccine safety.<sup>68</sup> This CDC project has been described elsewhere.<sup>68</sup> Monitoring for 9vHPV has begun as these sites transition completely from use of 4vHPV. For 9vHPV, near real-time post-licensure surveillance for several pre-specified outcomes will be conducted through Rapid Cycle Analysis.<sup>69</sup> The outcomes include anaphylaxis, allergic reactions, appendicitis, GBS, seizure, stroke, syncope, VTE, pancreatitis, and injection site reactions.<sup>13</sup> Because the label for 9vHPV mentions a possible increase for spontaneous abortion following 9vHPV when compared to 4vHPV, the VSD plans to conduct an evaluation of this outcome.<sup>5,13</sup>

The FDA's Sentinel System is a national, integrated, electronic system that allows for monitoring medical product safety on more than 178 million covered lives.<sup>70,71</sup> The Post-Licensure Rapid Immunization Safety Measurement (PRISM) program is a component of the Sentinel System specifically focusing on vaccines and links health plan data with state and city immunization registries. FDA's Sentinel System's pharmacovigilance plan for 9vHPV will monitor adverse events occurring after vaccination at the population level. This goal will be accomplished by a general safety study with multiple components, including 1) real-time active surveillance of several predetermined outcomes of interest and 2) surveillance for serious, unexpected events. Additionally, the Sentinel System will be used to conduct a study to examine the risk of spontaneous abortion when the vaccine is inadvertently administered to pregnant women.<sup>72</sup>

As part of Merck's post-marketing commitments, as outlined in FDA's approval letter for 9vHPV, 4 studies must be conducted.<sup>73</sup> To assess long term safety, immunogenicity, and effectiveness, two 10-year studies will be conducted. One study will be conducted among males and females aged 9–15 years and the other will include only females aged 16–26 years. Another post-marketing requirement is to conduct an observational study to further characterize the safety profile in approximately 10,000 persons. Lastly, a pregnancy registry has been developed to prospectively collect data on reported exposures occurring within 30 days prior to the last menstrual period or any time during pregnancy.

## Discussion

Data from the United States and other countries have provided a robust evaluation of 4vHPV safety. While studies have indicated a favorable safety profile, some national immunization programs have faced real and potential public losses of confidence in their programs as a result of increased negative publicity, even from safety issues that have been discounted in the literature. Safety findings for 4vHPV have been reassuring with no confirmed safety signals identified. However, despite the availability of a large body of data establishing the safety of 4vHPV, safety remains one of the top concerns among US parents whose children have not yet initiated HPV vaccination and is considered a barrier to vaccination by some physicians.

Specific parental safety concerns include the perceived lack of sufficient post-licensure safety data, the possibility of the vaccine causing side effects, and lasting health problems. Parental concerns about the safety and side effects of HPV vaccine have been found to be a negative predictor of vaccine initiation. In addition, publicized isolated media reports regarding select adverse events following HPV influence attitudes and behaviors regarding vaccination.<sup>74</sup>

The safety of HPV vaccines has been reviewed by the Institute of Medicine (IOM) and the World Health Organization (WHO). In 2011, the IOM published a report entitled “Adverse Events of Vaccines: Evidence and Causality.”<sup>75</sup> Through an in-depth review of epidemiologic and mechanistic evidence from peer-reviewed literature the IOM assessed relationships between specific health outcomes and eight vaccines, including HPV vaccines. The report accepted a causal relationship between HPV and anaphylaxis, but did not find evidence to support a relationship with 12 other outcomes examined. The report also found a causal relationship between syncope and all injected vaccines.

The WHO’s Global Advisory Committee on Vaccine Safety (GACVS) frequently reviews the safety of HPV vaccine, based on the available data, most recently in 2015.<sup>76</sup> In 2014, GACVS published a report to summarize the work of GACVS over the past six years in reviewing the safety of HPV vaccines.<sup>77</sup> In this report, based on the careful review of the available data, GACVS concluded that the benefit-risk profile remains favorable. Data from ongoing and published HPV studies are also regularly presented to advisory committees in the United States including ACIP and the Pediatric Advisory Committee of FDA.

9vHPV vaccine is similar to 4vHPV in its manufacturing processes and content, and safety data reviewed in this paper are reassuring. However, CDC, FDA, and public health and regulatory agencies in other countries continuously monitor safety of all vaccines in use. With the introduction of 9vHPV in the United States, the safety of this vaccine too will be assessed through passive surveillance, active surveillance, and special studies. Close monitoring of 9vHPV safety will ensure rapid availability of needed information for immunization programs and the public. Only with timely vaccine safety information can vaccination programs earn the public trust needed to achieve high coverage with these cancer-preventing vaccines.

### Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of CDC.

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