9

Human Papillomavirus Vaccine

INTRODUCTION

Human papillomaviruses (HPVs) represent a family of more than 100 nonenveloped, double-stranded DNA viruses uniquely targeted to the human epithelial cells (de Villiers et al., 2004; Schiller et al., 2008). HPVs are numbered in order of discovery and can be classified into groups according to the anatomic areas they infect (de Villiers et al., 2004; Schiller et al., 2008). Common, plantar, and juvenile or flat warts are caused by HPV1 and HPV2 (Bonnez and Reichman, 2010). These warts are common among the general population and are most common in children (Bonnez and Reichman, 2010). Genital warts and high-risk genital HPV infections, caused by HPV6 and 11 and HPV16, 18, 33, and 65 respectively, occur in an estimated 6.2 million people every year in persons aged 14 to 44 years, 74 percent among individuals between 15 and 24 years (Schiller et al., 2008; Weinstock et al., 2004).

HPV is transmitted through direct contact with the lesions or warts that develop as a result of HPV infection (Bonnez and Reichman, 2010). Genital HPV infections may be spread by penetrative intercourse and non-penetrative encounters such as oral-genital, manual-genital, and genital-genital interaction (Marrazzo et al., 2000; Winer et al., 2003). According to Schiller et al. (2008), up to 70 percent of sexually active young women will be infected with at least one HPV within the first 5 years of initial sexual encounter. The risk of infection increases with instances of sexual activity and the number of lifetime sexual partners. Manhart et al. (2006) indicated that among women 18 to 25, 14.3 percent with one lifetime sexual partner,
22.3 percent with two lifetime sexual partners, and 31.5 percent with three or more lifetime sexual partners experience at least one HPV infection.

HPV infection is often asymptomatic, but it may lead to the presence of cervical lesions or warts in some individuals. HPV infection is considered transient and usually lasts between 4 and 20 months in healthy individuals (Trottier and Franco, 2006). High-risk types of HPV such as HPV16 and HPV18 carrying the greatest risk of persistent infection constitute the most important risk factor for cervical cell abnormalities and invasive cervical cancer (Molano et al., 2003). Various approaches such as cryotherapy, electrocautery, surgical excision, and topical therapies have been used to treat HPV-associated lesions and warts (CDC, 2002).

Research and development of an HPV vaccine was spurred by evidence that inactivated bovine papillomavirus (BPV) could immunize cattle against BPV infection in the 1980s (Jarrett et al., 1990). However, owing to the oncogenic nature of HPV, live attenuated or inactivated vaccines could not be safely developed for humans (Schiller et al., 2008). In the 1990s, researchers found that inoculation with virus-like particles (VLPs) developed from the L1 protein of specific papillomaviruses (PVs) could protect against PV infection, but the protection is not universal for all HPVs (Schiller and Lowy, 1996).

Currently, two vaccines are licensed in the United States to prevent diseases caused by HPV infection. The quadrivalent vaccine, Gardasil (Merck & Co., Inc.) (HPV4), was licensed in 2006 by the Food and Drug Administration (FDA) to protect girls and women age 9 through 26 against anogenital warts and cancers (vulvar, vaginal, cervical, and anal) caused by HPV6, 11, 16, and 18 (CDC, 2007). Each 0.5 mL dose contains 20 µg each of HPV 6 and HPV 18 L1 protein and 40 µg each of HPV 11 and HPV 16 L1 protein (CDC, 2007). It also contains 225 µg of amorphous aluminum hydroxyphosphate sulfate (adjuvant), sodium chloride, L-histidine, polysorbate 80, sodium borate, and water (CDC, 2007). In 2009, Gardasil was also approved for use in males aged 9–26 years for the prevention of anal cancer and genital warts; however, although it is licensed for use in the same schedule and composition, as of May 2010, the Advisory Committee on Immunization Practices did not recommend routine vaccination in this population (CDC, 2010b). The bivalent vaccine, Cervarix (GlaxoSmithKline Biologicals) (HPV2), was also licensed in 2009 by the FDA to protect girls and women age 10 through 25 against HPV 16 and 18 (CDC, 2010a). Each dose of Cervarix is 0.5 mL and contains 20 µg each of HPV 16 and HPV 18 as well as 500 µg of aluminum hydroxide, 50 µg of 3-O-desacyl-4’-monophosphoryl lipid A (adjuvant), sodium chloride, sodium dihydrogen phosphate dehydrate, and water (CDC, 2010a). Both vaccines are recommended in a three-dose series of intramuscular
inoculations with the second and third dose administered 2 and 6 months after the first dose (CDC, 2010a). Both vaccines protect against 70 percent of HPV16 and 18 associated cancers, with Gardasil providing additional protection against 80 to 90 percent of genital wart–causing HPV infections (Bonnez and Reichman, 2010; CDC, 2010a). In 2009, 44.3 percent of girls in the United States aged 13 to 17 had received at least an initial dose of either the HPV4 or HPV2 vaccine (CDC, 2010c).

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of acute disseminated encephalomyelitis (ADEM) after the administration of HPV vaccine.

Weight of Epidemiologic Evidence

The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and ADEM.

Mechanistic Evidence

The committee identified four publications reporting ADEM after administration of HPV vaccine. The publications did not provide evidence beyond temporality (Borja-Hart et al., 2009; Mendoza Plasencia et al., 2010; Schaffer et al., 2008; Wildemann et al., 2009). In addition, Borja-Hart et al. (2009) intimated that in some cases multiple vaccines were administered concomitantly, making it difficult to determine which, if any, vaccine could have been the precipitating event. The publications did not contribute to the weight of mechanistic evidence.

Weight of Mechanistic Evidence

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of ADEM. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of ADEM; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

The committee assesses the mechanistic evidence regarding an association between HPV vaccine and ADEM as lacking.
Causality Conclusion

Conclusion 9.1: The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and ADEM.

TRANSVERSE MYELITIS

Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of transverse myelitis after the administration of HPV vaccine.

Weight of Epidemiologic Evidence

The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and transverse myelitis.

Mechanistic Evidence

The committee identified two publications reporting the development of transverse myelitis after administration of HPV vaccine. The publications did not provide evidence beyond temporality (Borja-Hart et al., 2009; Slade et al., 2009). In addition, Borja-Hart et al. (2009) intimated that in some cases multiple vaccines were administered concomitantly, making it difficult to determine which, if any, vaccine could have been the precipitating event. The publications did not contribute to the weight of mechanistic evidence.

Weight of Mechanistic Evidence

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of transverse myelitis. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of transverse myelitis; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

The committee assesses the mechanistic evidence regarding an association between HPV vaccine and transverse myelitis as lacking.

Causality Conclusion

Conclusion 9.2: The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and transverse myelitis.
NEUROMYELITIS OPTICA

Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of neuromyelitis optica (NMO) after the administration of HPV vaccine.

Weight of Epidemiologic Evidence

*The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and NMO.*

Mechanistic Evidence

The committee identified one publication reporting the development of neuromyelitis optica after administration of HPV vaccine. Borja-Hart et al. (2009) do not provide evidence beyond temporality. In addition, the authors intimate that in some cases multiple vaccines were administered concomitantly, making it difficult to determine which, if any, vaccine could have been the precipitating event. The publication did not contribute to the weight of mechanistic evidence.

Weight of Mechanistic Evidence

The symptoms described in the publication described above are consistent with those leading to a diagnosis of NMO. Autoantibodies, T cells, complement activation, and molecular mimicry may contribute to the symptoms of NMO; however, the publication did not provide evidence linking these mechanisms to HPV vaccine.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and NMO as lacking.*

Causality Conclusion

Conclusion 9.3: The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and NMO.
MULTIPLE SCLEROSIS

Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of multiple sclerosis (MS) after the administration of HPV vaccine.

Weight of Epidemiologic Evidence

_The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and MS._

Mechanistic Evidence

The committee identified two publications reporting MS developing after administration of HPV vaccine. One publication did not provide clinical, diagnostic, or experimental evidence, including the time frame between administration of HPV vaccine and development of symptoms (Verstraeten et al., 2008). Sutton et al. (2009) did not provide evidence beyond temporality that for some cases was too short based on the possible mechanisms involved. The publications did not contribute to the weight of mechanistic evidence.

Weight of Mechanistic Evidence

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of MS. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of MS; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

_The committee assesses the mechanistic evidence regarding an association between HPV vaccine and MS as lacking._

Causality Conclusion

Conclusion 9.4: The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and MS.
GUILLAIN-BARRÉ SYNDROME

Epidemiologic Evidence

The committee reviewed three studies to evaluate the risk of Guillain-Barré syndrome (GBS) after the administration of HPV vaccine. These three studies (Borja-Hart et al., 2009; Slade et al., 2009; Souayah et al., 2010) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

Weight of Epidemiologic Evidence

The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and GBS.

Mechanistic Evidence

The committee identified three publications reporting GBS after administration of HPV vaccine. One publication did not provide clinical, diagnostic, or experimental evidence, including the time frame between administration of HPV vaccine and development of symptoms (Verstraeten et al., 2008). Two publications did not provide evidence beyond temporality (Borja-Hart et al., 2009; Slade et al., 2009). In addition, two publications reported the concomitant administration of vaccines, in some cases making it difficult to determine which, if any, vaccine could have been the precipitating event (Borja-Hart et al., 2009; Slade et al., 2009). The publications did not contribute to the weight of mechanistic evidence.

Weight of Mechanistic Evidence

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of GBS. Autoantibodies, complement activation, immune complexes, T cells, and molecular mimicry may contribute to the symptoms of GBS; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

The committee assesses the mechanistic evidence regarding an association between HPV vaccine and GBS as lacking.
Causality Conclusion

Conclusion 9.5: The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and GBS.

CHRONIC INFLAMMATORY DISSEMINATED POLYNEUROPATHY

Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of chronic inflammatory disseminated polyneuropathy (CIDP) after the administration of HPV vaccine.

Weight of Epidemiologic Evidence

*The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and CIDP.*

Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of CIDP after administration of HPV vaccine.

Weight of Mechanistic Evidence

Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of CIDP; however, the committee did not identify literature reporting evidence of these mechanisms after administration of HPV vaccine.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and CIDP as lacking.*

Causality Conclusion

Conclusion 9.6: The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and CIDP.

BRACHIAL NEURITIS

Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of brachial neuritis after the administration of HPV vaccine.
Weight of Epidemiologic Evidence

The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and brachial neuritis.

Mechanistic Evidence

The committee identified two publications reporting brachial neuritis after administration of HPV vaccine. The publications did not provide evidence beyond temporality, some too long (Gardasil—Brachial plexus neuritis, 2009; Debeer et al., 2008). Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. The publications did not contribute to the weight of mechanistic evidence.

Weight of Mechanistic Evidence

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of brachial neuritis. Autoantibodies, T cells, and complement activation may contribute to the symptoms of brachial neuritis; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

The committee assesses the mechanistic evidence regarding an association between HPV vaccine and brachial neuritis as lacking.

Causality Conclusion

Conclusion 9.7: The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and brachial neuritis.

AMYOTROPHIC LATERAL SCLEROSIS

Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of amyotrophic lateral sclerosis (ALS) after the administration of HPV vaccine.

Weight of Epidemiologic Evidence

The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and ALS.
Mechanistic Evidence

The committee identified one publication and one abstract reporting the development of ALS after administration of HPV vaccine. Slade et al. (2009) did not provide clinical, diagnostic, or experimental evidence including the time frame between administration of vaccine and development of symptoms. This publication did not contribute to the weight of mechanistic evidence.

Huang et al. (2009), in an abstract, described a 14-year-old girl presenting with a rapidly progressing motor neuron disease 2 months after administration of the third dose of the HPV vaccine Gardasil. Despite treatment the patient’s weakness progressed leading to her death from respiratory failure 23 months after vaccination. Laboratory examinations revealed infiltrates of macrophages and T lymphocytes in the grey and white matter of the spinal cord and demyelination and loss of motor neurons. The patient was diagnosed with a rapidly progressive form of juvenile ALS.

Further investigation revealed that the patient expressed a point mutation in the fused in sarcoma/translocated in liposarcoma (FUS/TLS) gene leading to an amino acid substitution in a highly evolutionarily conserved region of the protein (Huang et al., 2010). Immunohistochemistry staining of motor neurons from the spinal cord revealed strongly FUS-positive basophilic inclusions in the patient. In contrast, patients with late-onset ALS showed no FUS-positive inclusions in motor neurons from the spinal cord. Similar basophilic inclusions were observed in the reticular formation in the medulla oblongata, red nucleus, nucleus ambiguous, sensorimotor cortex, and frontal cortex in the patient.

Based on the genetic analysis and neuropathology, the authors did not attribute the rapidly progressive form of juvenile ALS in the patient to vaccination against HPV using the quadrivalent vaccine Gardasil.¹

Weight of Mechanistic Evidence

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of ALS. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of ALS; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and ALS as lacking.*

¹C. Lomen-Hoerth, ALS Center, University of California San Francisco, personal communication, November 11, 2010.
Causality Conclusion

Conclusion 9.8: The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and ALS.

ANAPHYLAXIS

Epidemiologic Evidence

The committee reviewed three studies to evaluate the risk of anaphylaxis after the administration of HPV vaccine. These three studies (Brotherton et al., 2008; Kang et al., 2008; Slade et al., 2009) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

Weight of Epidemiologic Evidence

The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and anaphylaxis.

Mechanistic Evidence

The committee identified three publications describing clinical, diagnostic, or experimental evidence of anaphylaxis after administration of HPV vaccine. Kang et al. (2008) identified individuals suspected of developing a hypersensitivity reaction after administration of HPV vaccine; however, hypersensitivity reactions were not observed upon the subsequent administration of additional doses of HPV vaccine. This publication did not contribute to the weight of mechanistic evidence.

Described below are two publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Brotherton et al. (2008) conducted telephone interviews with patients, the patients’ guardians, and witnesses of adverse reactions to the HPV vaccine Gardasil in Australian school children. The authors reported eight cases of anaphylaxis in detail. Anaphylaxis developed in less than 5 minutes in four cases, 5–10 minutes in three cases, and 10–15 minutes in one case.

Slade et al. (2009) analyzed reports on the HPV vaccine Gardasil received by the Vaccine Adverse Event Reporting System (VAERS) from June 2006 through December 2008. The authors identified 28 reports of anaphylaxis, according to the Brighton case definition, after vaccination with Gardasil.
Weight of Mechanistic Evidence

The publications described above presented clinical evidence sufficient for the committee to conclude the vaccine may be a contributing cause of anaphylaxis after administration of HPV vaccine. The clinical descriptions establish a strong temporal relationship between administration of the vaccine and the anaphylactic reaction.

The committee assesses the mechanistic evidence regarding an association between HPV vaccine and anaphylaxis as intermediate based on 36 cases presenting temporality and clinical symptoms consistent with anaphylaxis.

Causality Conclusion

Conclusion 9.9: The committee concludes that the evidence favors acceptance of a causal relationship between HPV vaccine and anaphylaxis.

TRANSIENT ARTHRALTIA

Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of arthralgia after the administration of HPV vaccine. This one controlled study (Bhatla et al., 2010) contributed to the weight of epidemiologic evidence and is described below.

Bhatla et al. (2010) conducted a double-blind, randomized controlled trial in women (18 to 35 years of age) enrolled at four hospitals in India from July 2006 through March 2007. The patients were randomized in 1:1 ratio to receive HPV vaccine or placebo, and were given three doses at 0, 1, and 6 months. Diary cards were used to record any general symptoms that occurred during the 0–6 days following each dose. A total of 354 women were enrolled in the study and randomized to the vaccine group (176 women) or the placebo group (178 women). The safety analysis included patients who received at least one vaccine (167 women) or one placebo (170 women) during the study period. The diary cards were completed by 97.5 percent of the vaccine group and 98.1 percent of the placebo group. The incidence of arthralgia was similar among the two groups (approximately 10 percent of the women in both groups reported arthralgia); however, the study size and short-term follow-up make it difficult to draw conclusions.
Weight of Epidemiologic Evidence

The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between HPV vaccine and transient arthralgia.

Mechanistic Evidence

The committee identified two publications reporting arthralgia after administration of HPV vaccine. The publications did not provide evidence beyond temporality (Garcia-Sicilia et al., 2010; Rivera Medina et al., 2010). In addition, Garcia-Sicilia et al. (2010) also reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event. Neither publication reported the persistence of symptoms after vaccination. The publications did not contribute to the weight of mechanistic evidence.

Weight of Mechanistic Evidence

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of transient arthralgia. Autoantibodies, T cells, complement activation, and immune complexes may contribute to the symptoms of transient arthralgia; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

The committee assesses the mechanistic evidence regarding an association between HPV vaccine and transient arthralgia as lacking.

Causality Conclusion

Conclusion 9.10: The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and transient arthralgia.

PANCREATITIS

Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of pancreatitis after the administration of HPV vaccine. This study (Slade et al., 2009) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.
Weight of Epidemiologic Evidence

The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and pancreatitis.

Mechanistic Evidence

The committee identified two publications reporting pancreatitis after administration of HPV vaccine. Das et al. (2008) did not provide evidence beyond temporality. Slade et al. (2009) reported the development of pancreatitis in nine cases submitted to VAERS from June 2006 through December 2008. Two cases developed pancreatitis after the first dose and experienced a recurrence of symptoms after the second and third doses. However, the authors did not report the time frame between administration of the vaccine and development of pancreatitis; long latencies make it impossible to rule out other possible causes. In addition, all of the cases had preexisting risk factors for pancreatitis. The publications did not contribute to the weight of mechanistic evidence.

Weight of Mechanistic Evidence

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of pancreatitis, but the only evidence that could be attributable to the vaccine was recurrence of symptoms upon vaccine rechallenge; however, when reported without indicating the latency between vaccination and symptoms, these cases would not be considered cases of rechallenge. Antibodies and complement activation may contribute to the symptoms of pancreatitis; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

The committee assesses the mechanistic evidence regarding an association between HPV vaccine and pancreatitis as lacking.

Causality Conclusion

Conclusion 9.11: The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and pancreatitis.
THROMBOEMBOLIC EVENTS

Epidemiologic Evidence

The committee reviewed two studies to evaluate the risk of thromboembolic events after the administration of HPV vaccine. These two studies (Borja-Hart et al., 2009; Slade et al., 2009) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

Weight of Epidemiologic Evidence

The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and thromboembolic events.

Mechanistic Evidence

The committee identified two publications reporting thromboembolic events after administration of HPV vaccine. The publications did not provide evidence beyond temporality, some too short or too long based on the possible mechanisms involved (Borja-Hart et al., 2009; Slade et al., 2009). Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. In addition, all of the cases reported in the publications had predisposing risk factors for thromboembolic events including, but not limited to, pregnancy, the use of oral contraceptives, inherited hypercoagulability syndromes, and an aneurysm. The publications did not contribute to the weight of mechanistic evidence.

Weight of Mechanistic Evidence

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of thromboembolic events. Alterations in the coagulation cascade may contribute to the symptoms of thromboembolic events; however, the publications did not provide evidence linking this mechanism to HPV vaccine.

The committee assesses the mechanistic evidence regarding an association between HPV vaccine and thromboembolic events as lacking.
Causality Conclusion

Conclusion 9.12: The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and thromboembolic events.

HYPERCOAGULABLE STATES

Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of hypercoagulable states after the administration of HPV vaccine.

Weight of Epidemiologic Evidence

The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and hypercoagulable states.

Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of hypercoagulable states after administration of HPV vaccine.

Weight of Mechanistic Evidence

Alterations in the coagulation cascade may contribute to the symptoms of hypercoagulable states; however, the committee did not identify literature reporting evidence of this mechanism after administration of HPV vaccine.

The committee assesses the mechanistic evidence regarding an association between HPV vaccine and hypercoagulable states as lacking.

Causality Conclusion

Conclusion 9.13: The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and hypercoagulable states.

CONCLUDING SECTION

Table 9-1 provides a summary of the epidemiologic assessments, mechanistic assessments, and causality conclusions for HPV vaccine.
### TABLE 9-1  Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for HPV Vaccine

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Adverse Event</th>
<th>Epidemiologic Assessment</th>
<th>Studies Contributing to the Epidemiologic Assessment</th>
<th>Mechanistic Assessment</th>
<th>Cases Contributing to the Mechanistic Assessment</th>
<th>Causality Conclusion</th>
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<tbody>
<tr>
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<td>HPV</td>
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<td>Hypercoagulable States</td>
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</tr>
</tbody>
</table>
REFERENCES


HUMAN PAPILLOMAVIRUS VACCINE


