A cross-sectional study of the relationship between reported human papillomavirus vaccine exposure and the incidence of reported asthma in the United States

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Abstract

Objectives: Asthma is a chronic disorder that affects persons of all ages impacting the quality of their lives. This cross-sectional hypothesis-testing study evaluated the relationship between human papillomavirus vaccine and the risk of an incident asthma diagnosis in a defined temporal period post-vaccination.

Methods: The 2015–2016 National Health and Nutrition Examination Survey data were examined for a group of 60,934,237 weighted persons between 9 and 26 years old in Statistical Analysis Software.

Results: Reported incident asthma significantly clustered in the year of reported human papillomavirus vaccination. When the data were separated by gender, the effects observed remained significant for males but not females.

Conclusion: The results suggest that human papillomavirus vaccination resulted in an excess of 261,475 asthma cases with an estimated direct excess lifetime cost of such persons being US$42 billion. However, it is unclear what part of the vaccine and/or vaccine medium may have increased an individual's susceptibility to an asthma episode, whether the asthma diagnosis represented one asthma episode or if it is chronic, and how much therapeutic support was needed (if any) and for how long, which would impact cost. Despite the negative findings in this study, routine vaccination is an important public health tool, and the results observed need to be viewed in this context.

Introduction

Asthma is a chronic disorder that affects persons of all ages with potentially devastating consequences. It is associated with recurrent symptoms of difficulty breathing, wheezing, chest tightness, and coughing (particularly at night).[1] It was previously estimated that globally about 235 to 334 million persons suffer from asthma and it is responsible for about 250,000 deaths annually.[2] The World Health Organization (WHO) reports that asthma is the most common chronic condition diagnosed among children around the world.[3] A recent longitudinal study identified a number of demographic and neonatal risk factors for childhood asthma in the United States. It was revealed that gender (males more than females) and ethnicity (Black > Hispanic > Native American > Asian > White) were important mediating factors in the risk of a childhood asthma diagnosis. These findings suggest that genetic variation/susceptibility interacting with environmental factors may be of importance in the pathogenesis of asthma, and the study concluded that environmental factors should be examined for their potential contribution to the risk of being diagnosed with asthma.[4]

Asthma has a significant impact on quality of life, work and school productivity, use of health care, and in the worst cases it can result in death. As a consequence of the large societal economic burden of asthma, identifying potential

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causes of asthma is important for policy makers in setting priorities for public health programs.[1]

In light of the public health importance of identifying potential risk factors for asthma diagnoses, this study examined the National Health and Nutrition Examination Survey (NHANES) data. The NHANES is a major program of the National Center for Health Statistics (NCHS) of the US Centers for Disease Control and Prevention (CDC) designed to assess the health and nutritional status of adults and children in the United States. As described by NCHS, NHANES is supposed to be used in epidemiological studies to determine the prevalence of major diseases and risk factors for diseases, which help develop sound public health policy.

In light of the generally recognized significant immunological component to the etiology of asthma[2] and the theoretical reasons to suspect a possible association between asthma with vaccination,[5] this study evaluated the potential relationship between reported human papillomavirus (HPV) vaccine exposure and the risk of subsequently receiving a reported asthma diagnosis using the 2015–2016 NHANES data. The 2015–2016 NHANES data were examined because in June 2006, a vaccine, GARDASIL® (Merck & Co, Inc., Whitehouse Station, NJ, USA), which is to prevent HPV types 6, 11, 16, and 18, was approved by the US Food and Drug Administration (FDA). The vaccine was approved for use in females 9 through 26 years of age. In October 2009, the US FDA approved use of another HPV vaccine, CERVARIX® (GlaxoSmithKline Biologics, Research Triangle, NC, USA), which is used to prevent HPV types 16 and 18 in females from 10 through 25 years of age. In addition, the US FDA in October 2009 approved use of Gardasil vaccine in males 9 to 26 years of age. In February 2015, the 9-valent HPV vaccine known as Gardasil 9 was approved by the US FDA and recommended for use in both males and females. Gardasil 9 is used to provide protection against HPV 6, 11, 16, and 18 with additional protection against HPV 31, 33, 45, 52, and 58. Overall, from 2006 to the present, HPV vaccination completion rates have remained low among males (less than 21%) and females (less than 60%).[6] As a result, the 2015–2016 NHANES data provide one of the most current and best datasets to evaluate the potential relationship between reported HPV vaccine exposure and the risk of reported asthma.

The hypothesis tested in this study was that reported HPV vaccine exposure could significantly increase the risk of reported incident asthma diagnoses temporally related to HPV vaccine exposure. Then, based upon the results observed, additional analyses were undertaken to determine the numbers and costs associated with asthma diagnoses in the United States as a potential consequence of HPV vaccine administration and to determine whether gender was an important mediating factor.

Methods

This study employed the Statistical Analysis Software (SAS) system version 9.4 for Windows (Cary, NC, USA) running on a 64-bit-based PC with dual-core Intel® (Santa Clara, CA, USA) Xeon® CPU x5680 at 3.33 GHz, 6 cores, and 12 logical processors, with 44.0 GB of RAM and utilizing Microsoft (Redmond, WA, USA) Windows 7 Ultimate operating system to examine the NHANES data. The NHANES is a program of studies designed to assess annually the health and nutritional status of adults and children in the United States based on questionnaires and physical examinations and to track changes over time. The present study utilized demographic, socioeconomic, immunization, and health-related data within the NHANES database. The 2015–2016 NHANES was examined because it is the most current NHANES available. Persons 9 to 26 years of age were examined because HPV vaccine was approved for use in persons (males and females) 9 through 26 years of age.

Study participants

A total of 9971 persons (316,481,044 weighted persons) were examined from the 2015–2016 NHANES data. Among these persons, a subgroup of 2009 persons (60,934,237 weighted persons) between 9 and 26 years of age (age of vaccine receipt for reported HPV vaccine exposed persons and age of interview for reported HPV unexposed persons) with non-missing values for demographic, immunization, and medical condition variables were examined in this study.

Within the NHANES demographic dataset, the variables examined were as follows: gender (variable: RIAGENDR), age in years at screening (variable: RIDAGEYR), race (variable: RIDRETH3 (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, Hispanic, or Other), and socioeconomic status (variable: INDFMPIR (poverty income ratio (PIR)—a ratio of family income to poverty threshold)).

Outcomes

The NHANES medical conditions dataset was examined for reported asthma diagnosis status as follows. Each person included had a reported diagnostic status for the outcome of asthma (variable: MCQ010, survey question, "Has a doctor or other health professional ever told {you/study participant} that {you have/he or she/study participant has} asthma (az-ma)?") and a reported age when asthma was first diagnosed (variable: MCQ025, survey question, "How old {were you/ was study participant} when {you were/he or she was} first told {you/he or she} had asthma (az-ma)?"

The current health status of each person was also determined by evaluating the NHANES current health status dataset. Each person had a reported diagnostic status for the following outcomes: stomach or intestinal illness in the last 30 days (variable: HSQ510, "Did {you/study participant} have a stomach or intestinal illness with vomiting or diarrhea that started during those 30 days?") and head cold or chest cold within the last 30 days (variable: HSQ500, survey question, "Did {you/study participant} have a head cold or chest cold that started during those 30 days?"). The current health status outcomes were selected a

Table 1. An evaluation of the temporal relationship between reported asthma outcomes and reported HPV vaccine exposure.

Time period of exposure between reported age of reported asthma diagnosis and reported age of HPV vaccine exposure in years[a]	Total weighted number of reported HPV vaccine exposed persons with reported incident asthma	Total weighted number of reported HPV vaccine exposed persons	Reported asthma incidence rate per 100 reported HPV vaccine exposed weighted persons
0	299,245 (65.15%)	16,240,688	1.84
1	27,064 (5.89%)	14,907,617	0.18
2	76,192 (16.59%)	11,812,174	0.65
3	56,831 (12.37%)	9,454,420	0.60
Total	459,332 (100%)	–	–

HPV: human papillomavirus; NHANES: National Health and Nutrition Examination Survey.
[a]The time period between reported HPV vaccination and reported outcome was adjusted in the data to ensure that each person examined had the appropriate time period between vaccine exposure and the outcome (e.g. when studying the rate of reported asthma in the third year after reported HPV vaccination, all reported HPV vaccinated persons would have to have at least 3 years between exposure and the date of NHANES interview, so as to be able to capture reported asthma outcomes diagnosed 3 years after reported HPV vaccination.).

priori as not having a biologically plausible link to exposure to HPV vaccine and were selected to reflect the general health status of the exposed/unexposed persons examined.

Exposure

The immunization exposure variable was identified from within the NHANES immunization dataset. The variables examined were number of HPV vaccine doses (variable: IMQ100, survey question, "How many doses of {Cervarix/Gardasil/Gardasil or Gardasil 9/the vaccine} {have you/has study participant} received?") and age first dose of HPV vaccine (variable: IMQ090, survey question, "How old {were you/was study participant} when {you/study participant} received your first dose of {Cervarix/Gardasil/Gardasil 9/Gardasil or Gardasil 9/the vaccine}?"). Persons reported as receiving one, two, or three doses of HPV vaccine and a reported age for the first dose of HPV vaccine composed the exposed persons group (reported HPV vaccine exposed group). Persons in this group were selected to have a reported age of first dose of HPV vaccine between 9 and 26 years old. By contrast, persons reported as having received no doses of HPV vaccine composed the unexposed persons group (reported HPV vaccine unexposed group). Persons in this group were selected to have an age of NHANES examination (index age) between 9 and 26 years old. This index age in the reported HPV unexposed group was selected to ensure a comparable comparison relative to the reported age of first dose of HPV vaccine in the reported HPV vaccine exposed group. In addition, any persons identified within the reported HPV vaccine exposed group with reported asthma prior to the age of reported HPV vaccine receipt were also included in the reported HPV vaccine unexposed group.

Statistical analyses

The number of persons exposed/unexposed and the number of persons diagnosed with asthma were sufficient to allow

for adequate statistical power for the analyses undertaken in this study. In all statistical analyses, a two-sided p value <0.05 was considered statistically significant. The overall null hypothesis was that there would be no relationship between reported HPV vaccine exposure and the risk of any of the three reported outcomes studied—asthma, stomach or intestinal illness within the last 30 days, or head cold or chest cold within the last 30 days.

In the first statistical analysis undertaken, persons in the reported HPV vaccine exposed group were analyzed to determine the potential temporal clustering relationship between the reported age of the first dose of HPV vaccine exposure and the reported age of initial asthma diagnosis was evaluated. This analysis was done by subtracting the reported age at which the first dose of HPV vaccine was administered from the reported age at which asthma was first diagnosed. If the difference in age between the reported age of the first dose of HPV vaccine exposure and reported age of initial asthma diagnosis was zero, then it was assumed that they occurred in the same year (year=0). Overall, a total of 16,240,688 persons were in the HPV vaccine exposed group. In analyzing reported asthma age that occurred in the first year (year=1) after the reported age of the first dose of HPV vaccine exposure (e.g. reported age of initial asthma diagnosis–age of the first dose of HPV vaccine exposure=1), persons in the exposed HPV group were required to have their initial NHANES interview examination age at least 1 year after the reported age of the first dose of HPV vaccine exposure. This was done to allow for all persons in the HPV vaccine exposed group to have sufficient time following their HPV vaccine exposure to capture reported initial asthma diagnosis in the initial NHANES interview examination. As a consequence, the overall size of the HPV vaccine exposed group was 14,907,617 persons. This same type of analysis was undertaken for the second (year=2) and third (year=3) years post the reported first dose of HPV vaccine exposure. Table 1 provides an overview of the data analyzed in this study.

Table 2. A summary of the composition of the 60,934,237 weighted persons examined in this study.

Parameter examined	Reported HPV vaccine exposed persons (weighted n = 16,240,688)	Reported HPV unexposed persons (weighted n = 44,693,549)
Gender		
Male	4,742,781 (29.20%)	25,056,901 (56.06%)
Female	11,497,907 (70.80%)	19,636,648 (43.94%)
Age		
Mean age at HPV vaccination ± SD (range = 9–26 years old)	14.96 ± 3.61	–
Mean age at interview ± SD (range = 9–26 years old)	19.16 ± 5.37	17.51 ± 3.39
Race		
Non-Hispanic White	10,178,151 (62.67%)	24,618,719 (55.08%)
Non-Hispanic Black	1,964,127 (12.09%)	5,805,845 (12.99%)
Hispanic	2,738,126 (16.86%)	9,682,407 (21.66%)
Non-Hispanic Asian	825,908 (5.09%)	2,246,202 (5.03%)
Other	534,377 (3.29%)	2,340,375 (5.24%)
Diagnosis status		
Asthma	828,954 (5.10%)	12,210,425 (27.32%)
Stomach or intestinal illness	1,448,977 (8.92%)	3,590,809 (8.03%)
Head cold or chest cold	2,185,075 (13.45%)	8,476,619 (18.97%)
Socioeconomic status		
Mean PIR score ± SD	2.76 ± 1.55	2.45 ± 0.95

HPV: human papillomavirus; SD: standard deviation; PIR: poverty income ratio.

It was observed that the highest reported asthma incidence rate was when the reported first dose of HPV vaccine exposure and reported incident age of asthma diagnosis were in the same year with decreasing reported asthma incidence rates in subsequent years. In order to evaluate the temporal clustering of reported asthma following reported HPV vaccine exposure, binomial proportion modeling was utilized to compare the reported asthma incidence rate per 100 reported HPV vaccine exposed persons when they were reported to occur in the same year (1.84 per 100 reported HPV vaccine exposed persons) in comparison to the average reported asthma incidence rate per 100 reported HPV vaccine exposed persons for years 1, 2, and 3 post-HPV vaccine exposure (0.48 per 100 reported HPV vaccine exposed persons) or the average reported asthma incidence rate per 100 reported HPV vaccine exposed persons for years 2 and 3 post-HPV vaccine exposure (0.625 per 100 reported HPV vaccine exposed persons).

In the second statistical analysis undertaken, an evaluation of reported HPV vaccine exposed persons in comparison to reported HPV vaccine unexposed persons was evaluated. Table 2 provides a summary of the demographic composition of the persons examined in this study. Survey logistic regression modeling (stratum—variable: SDMVSTRA, cluster—variable: SDMVPSU, and weight—variable: WTINT2YR) was utilized to determine the potential relationship between reported exposure to HPV vaccine and the incidence of reported asthma at the same age without covariates (Model I—unadjusted). The data were analyzed overall and then separated by gender. Similarly, analyses using Model I were undertaken to evaluate the current health status outcomes of reported stomach or intestinal illness and reported head cold or chest cold. In addition, the covariates of age, gender, race, and socioeconomic status were also considered to evaluate the potential relationship between reported HPV vaccine exposure and the reported outcomes examined in this study (Model II—adjusted).

In the third statistical analysis undertaken, the incidence rate of reported asthma in the same year of reported HPV vaccine exposed persons in comparison to the incidence rate of reported asthma among reported HPV unexposed persons for a similar time period by survey frequency modeling (stratum—variable: SDMVSTRA, cluster—variable: SDMVPSU, and weight—variable: WTINT2YR) was evaluated. The data were analyzed overall and then separated by gender. The Rao–Scott χ^2 test statistic was employed to determine statistical significance.

Results

Table 1 examines the temporal relationship between the incidence rates of reported asthma following reported HPV vaccine exposure by year in the ensuing 3-year period post-immunization. It was observed that most persons with reported incident asthma were in the same year as reported HPV vaccine exposure (65.15%) with an incidence rate of reported asthma of 1.84 per 100 reported HPV vaccine exposed persons. The lowest portion of persons with reported incident asthma was in the year after reported HPV vaccine exposure (5.89%) with an incidence rate of reported asthma of 0.18 per 100 reported HPV vaccine exposed persons. Temporal clustering analysis using binomial proportion

Table 3. A summary of the logistic regression models generated to examine the potential relationship between reported HPV vaccine exposure and the risk of the three reported outcomes studied within the same year.

Model	Outcome	Variable	Odds ratio	95% confidence interval
	Reported asthma			
I		**HPV vaccine exposure**	**8.010**	**1.980–32.410**
II		**HPV vaccine exposure**	**9.726**	**2.911–32.490**
		Age	0.928	0.789–1.092
		Gender (female versus male)	0.336	0.096–1.182
		Hispanic versus non-Hispanic White	0.416	0.095–1.822
		Other versus non-Hispanic White	–	–
		Non-Hispanic Asian versus non-Hispanic White	1.287	0.261–6.362
		Non-Hispanic Black versus non-Hispanic White	0.319	0.063–1.609
		Socioeconomic status	**0.583**	**0.369–0.920**
	Reported stomach or intestinal illness			
I		HPV vaccine exposure	1.121	0.690–1.821
II		HPV vaccine exposure	1.091	0.643–1.850
		Age	1.005	0.961–1.051
		Gender (female versus male)	1.189	0.693–2.038
		Hispanic versus non-Hispanic White	0.989	0.686–1.427
		Other versus non-Hispanic White	0.473	0.151–1.481
		Non-Hispanic Asian versus non-Hispanic White	0.682	0.350–1.327
		Non-Hispanic Black versus non-Hispanic White	0.829	0.567–1.212
		Socioeconomic status	0.940	0.805–1.097
	Reported head cold or chest cold			
I		**HPV vaccine exposure**	**0.664**	**0.479–0.922**
II		**HPV vaccine exposure**	**0.594**	**0.437–0.807**
		Age	1.001	0.963–1.040
		Gender (female versus male)	**1.271**	**1.022–1.581**
		Hispanic versus non-Hispanic White	0.791	0.484–1.293
		Other versus non-Hispanic White	0.986	0.441–2.207
		Non-Hispanic Asian versus non-Hispanic White	**0.564**	**0.348–0.913**
		Non-Hispanic Black versus non-Hispanic White	0.866	0.548–1.369
		Socioeconomic status	**1.121**	**1.022–1.229**

HPV: human papillomavirus.
Bold-Italicized results are statistically significant at $p < 0.05$. Survey logistic modeling was employed to determine the relationship between reported vaccine exposure and reported outcome status in Model I = unadjusted for covariates and Model II = adjusted for the covariates of age, gender, race, and socioeconomic status.

modeling revealed that the frequency of reported incident asthma (1.84 per 100 reported HPV vaccine exposed persons) was significantly higher (risk ratio = 3.83, $p < 0.0001$) in the year of reported HPV vaccine than the average frequency of reported incident asthma in years 1, 2, and 3 post-HPV vaccine exposure (0.48 per 100 reported HPV vaccine exposed persons). Similarly, the frequency of reported incident asthma was also significantly higher (risk ratio = 2.94, $p < 0.001$) in the year of reported HPV vaccine than the average frequency of reported incident asthma in years 2 and 3 post-HPV vaccine exposure (0.625 per 100 reported HPV vaccine exposed persons).

Table 2 summarizes the demographic composition of the 60,934,237 weighted persons examined among the reported HPV vaccine group and the reported HPV unexposed group. Overall, there were 2.75-fold more persons in the reported

HPV vaccine unexposed group than in the reported HPV vaccine exposed group. It was observed that those in the reported HPV vaccine exposed group had a female preponderance (female/male ratio = 2.42), whereas the reported HPV vaccine unexposed group had a male preponderance (female/male ratio = 0.78). In addition, the reported HPV vaccine exposed group and the reported HPV vaccine unexposed group were similar with respect to socioeconomic status and ethnic composition.

Table 3 reveals the results of logistic regression models created to evaluate the potential relationship between reported HPV vaccine exposure and the risk of the three outcomes studied when they occurred within the same year. It was observed that the incidence of reported asthma was significantly increased by reported HPV vaccine exposure in the unadjusted (odds ratio = 8.010, 95% confidence interval = 1.980–32.410)

Table 4. A summary of the logistic regression models generated to examine the impact of gender on the potential relationship between reported HPV vaccine exposure and the risk of reported asthma studied within the same year.

Model	Gender	Variable	Odds ratio	95% confidence interval
	Females only			
I		HPV vaccine exposure	3.758	0.749–18.865
II		HPV vaccine exposure	4.138	0.752–22.777
		Age	***0.847***	***0.753–0.953***
		Hispanic versus non-Hispanic White	0.709	0.191–2.634
		Other versus non-Hispanic White	–	–
		Non-Hispanic Asian versus non-Hispanic White	1.920	0.207–17.838
		Non-Hispanic Black versus non-Hispanic White	0.480	0.061–3.785
		Socioeconomic status	***0.480***	***0.286–0.805***
	Males only			
I		***HPV vaccine exposure***	***18.994***	***2.736–131.848***
II		***HPV vaccine exposure***	***20.775***	***7.820–55.192***
		Age	1.008	0.833–1.219
		Hispanic versus non-Hispanic White	0.236	0.017–3.374
		Other versus non-Hispanic White	–	–
		Non-Hispanic Asian versus non-Hispanic White	0.920	0.086–9.876
		Non-Hispanic Black versus non-Hispanic White	0.228	0.017–2.976
		Socioeconomic status	0.632	0.333–1.197

HPV: human papillomavirus.
Bold-Italicized results are statistically significant at $p < 0.05$. Survey logistic modeling was employed to determine the relationship between reported vaccine exposure and reported outcome status in Model I = unadjusted for covariates and Model II = adjusted for the covariates of age, race, and socioeconomic status.

and adjusted (odds ratio = 9.726, 95% confidence interval = 2.911–32.490) models. By contrast, it was observed that reported stomach or intestinal illness within the last 30 days showed no relationship with reported HPV vaccine exposure in the unadjusted and adjusted models, and the risk of reported head cold or chest cold in the last 30 days was significantly reduced with reported HPV vaccine exposure in the unadjusted (odds ratio = 0.664, 95% confidence interval = 0.479–0.922) and adjusted (odds ratio = 0.594, 95% confidence interval = 0.437–0.807) models.

Table 4 shows the results of logistic regression models created to evaluate the impact of gender on the potential relationship between reported HPV vaccine exposure and the risk of the three outcomes studied when they occurred within the same year. It was observed that reported HPV vaccine exposure significantly increased the risk of reported asthma in unadjusted (odds ratio = 18.994, 95% confidence interval = 2.736–131.848) and adjusted (odds ratio = 20.775, 95% confidence interval = 7.820–55.192) models. By contrast, reported HPV vaccine exposure was not significantly associated with the risk of reported asthma in unadjusted or adjusted models.

Table 5 provides an overview of the results of survey frequency modeling used to evaluate the risk of reported incident asthma in the reported HPV vaccine exposure group in comparison to reported incident asthma in the reported HPV vaccine unexposed group within the same year. Among the male and female data combined, it was observed that reported

HPV vaccine exposure significantly increased the risk of reported incident asthma (risk ratio = 7.88, 95% confidence interval = 1.75–35.46) with an excess attributable rate = 0.0161. Therefore, from the population examined in this study, an excess of 261,475 persons with reported incident asthma at the same age as reported HPV vaccine exposure were attributably associated with reported HPV vaccine exposure. Subsequently, when the data were separated by gender, it was observed that the risk of reported incident asthma in the male reported HPV vaccine exposure group in comparison to reported incident asthma in the male reported HPV vaccine unexposed group within the same year was significantly increased (risk ratio = 19.01, 95% confidence interval = 2.31–156.25), whereas the risk of reported incident asthma in the female reported HPV vaccine exposure group in comparison to reported incident asthma in the female reported HPV vaccine unexposed group within the same year was not significantly different (risk ratio = 3.73, 95% confidence interval = 0.65–21.32).

Discussion

The results in this study provide the first epidemiological evidence supporting the hypothesis that reported HPV vaccine exposure significantly increased the risk of reported incident asthma. A significant association between reported HPV vaccine exposure and reported incident asthma was observed in temporal clustering, survey logistic, and survey

Table 5. A summary of the risk for reported asthma following reported HPV vaccine exposure in the same year.

Gender status	Exposure status	Total number of weighted persons with reported outcome (%)	Total number of weighted persons	Outcome measurements
Males and females				
	Reported HPV vaccine unexposed	104,518 (0.23%)	44,693,549	
	Reported HPV vaccine exposed	299,245 (1.84%)	16,240,688	
	Rate ratio (95% confidence interval)			*7.88 (1.75–35.46)*
	p value			*0.0005*
	Attributable rate			*0.0161*
Females only				
	Reported HPV vaccine unexposed	48,828 (0.25%)	19,636,648	
	Reported HPV vaccine exposed	106,723 (0.93%)	11,497,907	
	Rate ratio (95% confidence interval)			3.73 (0.65–21.32)
	p value			0.0806
	Attributable rate			0.0068
Males only				
	Reported HPV vaccine unexposed	55,691 (0.22%)	25,056,901	
	Reported HPV vaccine exposed	192,521 (4.06%)	4,742,781	
	Rate ratio (95% confidence interval)			*19.01 (2.31–156.25)*
	p value			*<0.0001*
	Attributable rate			*0.0384*

HPV: human papillomavirus.
Bold-italicized results are statistically significant at p < 0.05. Survey frequency modeling was utilized to evaluate the relationship between reported vaccine exposure and the reported outcome of asthma.

frequency modeling even when considering covariates such as age, gender, race, and socioeconomic status. It was observed that when the data were separated by gender, the effects remained significant among males but not females. By contrast, reported HPV vaccine exposure did not increase the risk of the current health status outcomes of stomach or intestinal illness with vomiting or diarrhea within the last 30 days or the outcome of head cold or chest cold within the last 30 days, which were selected a priori as not having a biologically plausible link to exposure to HPV vaccine.

The results observed in this study linking HPV vaccine exposure with asthma are biologically plausible. Investigators described that allergic asthma is widely recognized as the most common form of asthma among children and is estimated to be associated with 60% of all asthma cases.[2] The pathway leading to allergic asthma involves the initiation of inflammation by antigen-presenting cells promoting the production of type 2 helper (Th2) cells from naïve T lymphocytes. It is believed that Th2 cells then mediate the allergic asthma through proinflammatory cytokines—that is, interleukins (IL)-4, IL-5, IL-9, and IL-13—leading to the production of immunoglobulin E (IgE) early in the cascade and, later, eosinophils.[7]

It was previously described that vaccine antigens and/or their adjuvants have a direct IgE-potentiating effect.[8–11] It was also described that vaccine exposure may cause the immunologic balance to shift toward a more allergenic response.[12] In the case of HPV vaccine, it is important to consider that the vaccine is composed of multiple HPV antigens and an aluminum-based adjuvant. It is well established that HPV infection is known to promote Th2 cells and reduces Th1 cells,[13] and aluminum-based adjuvants are known to induce Th2 responses, which are characterized by IgE production.[14] Therefore, HPV vaccine contains constituent components that individually or synergistically have the potential to initiate immunological mechanisms capable of inducing allergic asthma in susceptible persons.

The results observed in this study also provide important insights into the potential general US population consequences of the increased risk of reported incident asthma following reported HPV vaccine. Specifically, it was observed in this study that an excess of 261,475 persons with reported incident asthma were attributably associated with HPV vaccine exposure. It was previously reported in a detailed analysis of the cost of the asthma in the United States that the direct cost of asthma was US$3259 per person per year.[1] Therefore, the annual cost to the United States of asthma attributably associated with HPV vaccine exposure from this study would be US$852,147,025, and assuming that such persons lived an average of 50 years, this would mean that the lifetime costs of such persons to the United States would be US$42,607,351,250.

It is important to consider, when evaluating the aforementioned costs attributably associated with HPV vaccine exposure in the United States, that the current study revealed that HPV vaccine uptake was only 26.65% among persons 9 to 26 years old. As a result, as continued public health efforts are undertaken to increase HPV vaccine uptake in the United

States, the costs attributably associated with HPV vaccine exposure in the United States will undoubtedly continue to rise. For example, if it was assumed that HPV vaccine uptake coverage reached 80% of the population 9 to 26 years old (this is a standard minimal goal for vaccine uptake percentage), the data from the present study would predict that an excess of 784,916 persons with asthma would be attributably associated to HPV vaccine exposure. This would mean that the annual cost to the United States of asthma attributably associated with HPV vaccine exposure would be US$2,558,041,244, and the cost to the United States over an average of a 50-year life span of such persons would be US$127,902,062,200. These numbers would be magnified even more assuming that eventually 80% of the whole US population was exposed to HPV vaccine. Specifically, this study examined an estimated 60,934,237 persons between 9 and 26 years of age, and it was estimated that there were a total of 316,481,044 persons in the whole US population. Therefore, applying an 80% HPV vaccine coverage to the entire US population, the data from the present study would predict that an excess of 4,076,707 persons with asthma would be attributably associated to HPV vaccine exposure. This would mean that the annual cost to the United States of asthma attributably associated with HPV vaccine exposure would be US$13,285,988,360, and the cost to the United States over an average of a 50-year life span of such persons would be US$664,299,418,000. It is important to note that the aforementioned modeling calculations assume a linear increase in the number of asthma cases with increasing HPV vaccine uptake, but it is unknown whether there is a cap on the number of susceptible persons or not.

It is also important when considering the aforementioned calculations about potential adverse effects associated with HPV vaccine administration that an estimated 12,000 women in the United States are diagnosed with cervical cancer every year, and currently licensed HPV vaccines in the United States are estimated to protect against HPV strains associated with more than 66% of cervical cancers.[15] In addition, it was revealed based upon analyses of NHANES data that HPV vaccine administration significantly reduced oral, genital, and cervical transmission of HPV in the United States by more than 80%.[16–18] Furthermore, an examination of the impact of HPV vaccine programs in 73 countries between 2001 and 2020 was estimated to result in the broader economic and social value of these vaccinations at US$820 billion.[19] Therefore, in light of the findings of potential adverse effects observed in the present study, and numerous previous studies showing effectiveness of HPV vaccine in reducing HPV transmission, the risk–benefit analysis of HPV vaccine is a complex issue and requires further examination in future studies.

Strengths/limitations

An important strength of this study was that NHANES data were examined. The NHANES examines a nationally representative sample of about 5000 Americans located in counties across the United States each year, combining interviews with physical and laboratory examinations. As described previously, the NCHS of the CDC has described that NHANES data are an important source for epidemiological data to help develop sound public health policy, and NHANES data were previously utilized to demonstrate the significant effectiveness of HPV vaccine administration to reduce HPV transmission in the United States.[16–18]

The collection of the NHANES data independently of the methods used in this study was another important strength. The different NHANES data elements were collected independently from one another (i.e. persons providing information about their asthma diagnosis status did not know that this would be related to information collected about HPV immunization status). As a result, phenomena such as selection bias for study participants, recall bias associating exposures with outcomes, or examiner bias should have minimally impacted the phenomena observed in this study.

A further strength of this study was the consistency, specificity, and magnitude of the results observed. It was consistently observed in this study that reported HPV vaccine exposure was associated with an increased risk of a reported incident asthma diagnosis. This phenomenon remained consistent when using different methods of data analysis (i.e. temporal cluster modeling, survey logistic regression modeling, or survey frequency modeling) or when statistical models with covariates such as age, race, gender, and socioeconomic status were employed. The specificity of the phenomenon observed in this study was further confirmed when the statistical models developed revealed no significant increased risk between reported exposure to HPV vaccine and the reported outcomes of stomach or intestinal illness within the last 30 days or reported head cold or chest cold in the last 30 days that were selected a priori as not being biologically plausibly linked to exposure to HPV vaccine. Finally, given that most p values observed were <0.01 and the limited number of statistical tests performed, it would seem unlikely that the results observed in this study were the result of statistical chance.

An additional strength of this study was that it was possible to evaluate a cause and effect relationship between reported HPV vaccine exposure and incident cases of reported asthma. It is unusual in cross-sectional studies to be able to examine a cause and effect relationships, but the NHANES data examined specifically reported the age at which persons were initially diagnosed with asthma, initially exposed to HPV vaccine, and interviewed by NHANES staff. As a result, it was possible to determine the temporal relationship between reported HPV vaccine exposure and reported asthma outcomes, and the temporal relationship between being interviewed by NHANES staff and asthma outcomes. It was hypothesized, and the results confirmed, that there was a significant increased risk for reported incident asthma outcomes within the first year post reported HPV vaccine exposure in comparison to the reported incidence rate of asthma outcomes after the first year post

reported HPV vaccine exposure. It should be noted that a temporal relationship between exposure and outcome is only one factor to consider in a potential causal relationship and does not necessarily establish causality.

A potential limitation of this study was the data collection methods utilized in the NHANES data examined. The outcomes examined in this study were based upon detailed survey questions asked of persons participating in the NHANES program. We did not formally assess an asthma diagnosis or immunization administration records. It is possible that participants may have recalled information erroneously (i.e. the diagnosis of asthma) or reported information inaccurately (i.e. receipt of HPV vaccine). Despite such limitations, it is presumed that such limitations/errors in the data examined would have applied equally to all the persons examined in this study. If anything, such errors in the data would have in all probability reduced the overall statistical power of this study to detect true significant relationships.

In addition, there is the potential for short-term recall bias (i.e. persons tend to recall exposures/outcomes that occurred more recently than further in the past) in the NHANES data examined. It was observed among persons reported as receiving HPV vaccine and subsequently being reported to have asthma, the mean elapsed time in years between the age of reported HPV vaccine receipt and the age of being interviewed in NHANES was 5.49 years (range = 1–10), and the age of reported asthma onset and the age of being interviewed in NHANES was 4.61 years (range = 0–10). Therefore, given the significant amount of time elapsed occurred between the age when persons were interviewed in NHANES and the reported age of HPV vaccine receipt or the reported age of asthma onset, it would seem that short-term recall bias of exposure/outcome variables limitedly impacted the data examined in this study.

A further potential limitation of this study was that the exact component of the HPV vaccine responsible for the effects observed was not specifically isolated. It is possible that the aluminum adjuvant or the antigen might be responsible or act synergistically to induce asthma. Future studies should continue to examine HPV vaccines to determine which vaccine components may be responsible for asthma outcomes.

In addition, a potential limitation of this study was that there may be differences in the general health status of reported HPV vaccine exposed persons in comparison to reported HPV unexposed persons. This may stem from the fact, as previously described by investigators from the CDC, that vaccination may be withheld from some persons precisely because they were at high risk of being diagnosed with the condition.[20] This type of "healthy vaccine" effect will likely underestimate the risk of vaccine associated adverse reactions. This phenomenon appears to be present in the data examined in this study because it was observed that the rate of reported head cold or chest cold within the last 30 days among persons receiving HPV vaccine exposure was significantly lower than among persons not receiving HPV vaccine exposure.

A further potential limitation of this study was that it was not possible to conduct analyses to explore the precise types of HPV vaccine and number of doses that might modify the observed significant association between reported HPV vaccination and reported incident asthma because these data were too limited in the dataset examined. It would be worthwhile in future studies to explore these phenomena in other databases. In addition, it is possible that other covariates may further mediate the relationships observed in this study. It would also be worthwhile in future studies to explore other potential covariates.

Another potential limitation of this study is that incident reported asthma after reported HPV vaccination may be coincidental and to not causally related to immunization. It was previously described by investigators that large-scale implementation of HPV vaccine programs would be followed by adverse events such as asthma occurring in temporal association with vaccine administration.[21] These investigators undertook a cohort study of female adolescents and young adults in the pre-HPV vaccine era to estimate the risks of coincident associations between HPV vaccine administration and adverse outcomes. These investigators reported that demand for an emergency room consultation often reflects either a recent onset or a recent exacerbation of a preexisting condition, both situations that inevitably lead to a search for putative precipitating events. These investigators reported that immune-mediated conditions were the third most common cause for an emergency room consultation in adolescent girls and that asthma conditions ranked first among atopic/allergic conditions with a rate of asthma conditions occurring at 325 per 100,000 emergency room consultations. As a result, great care was taken in the present study to attempt to minimize the potential for coincidental asthma following HPV immunization. First, this study examined the incidence of reported asthma to ensure that the persons examined did not have asthma previously that simply by happenstance had another flare in the post-vaccination period. Second, this study examined the temporal clustering of reported incident asthma in reported HPV vaccinated persons. This helped to ensure that whatever factors were associated with HPV vaccine receipt were held constant, and the only variable was how long after the immunization cases of reported incident asthma were counted. It was revealed that there was a significant temporal clustering of reported incident asthma in the year post-HPV vaccination in comparison to later periods post-HPV vaccination. Finally, a comparison was made for the relative frequency of reported incident asthma in HPV vaccine exposed persons in comparison to HPV unexposed persons over a similar time period. It was observed that there was a significant increase in the frequency of reported incident asthma in HPV vaccine exposed persons in comparison to HPV unexposed persons, but not for the rate of other conditions selected a priori as not being biologically plausibly linked to HPV vaccine exposure.

Another potential study limitation is that there may be other subcauses in the stated asthma cases. Also unclear is

what part of the vaccine and/or the vaccine medium may have increased an individual's susceptibility to an asthma episode, whether the asthma diagnosis represented one asthma episode or if it is chronic, and how much therapeutic support was needed (if any) and for how long, which would impact cost.

A final potential limitation of this study was that there may be statistical power limitations in the data examined by gender. It was observed that when the data examined were separated by gender, the asthma effects observed in this study remained significant among males but not females. It is possible that when separating the data by gender, the statistical power of the present study was significantly reduced, and, as a consequence, potentially significant relationships were missed. It is recommended that future studies further evaluate the potential interaction between gender and HPV vaccine associated adverse effects.

Conclusion

This cross-sectional study provides the first epidemiological evidence suggesting a significant relationship between HPV vaccine administration and the risk of an incident asthma diagnosis within the first-year post-immunization. It was estimated that HPV vaccine administration to persons aged 9 to 26 years old in the US population was attributably associated with an excess of 261,475 asthma cases with an estimated direct excess lifetime cost of such persons being US$42 billion. It was also found that when the data were separated by gender, the effects remained significant for males but not females. Despite the negative findings in this study, routine vaccination is an important public health tool to prevent infectious diseases[22] and routine HPV vaccine administration was reported to have significant benefits.[15–18] Therefore, the results observed in this study need to be evaluated within this context. Future studies should be undertaken to further evaluate the potential relationship between HPV vaccine administration and the risk of asthma in other databases to provide a more clear understanding of what, if any, adverse effects are associated with HPV vaccine, so that HPV vaccine programs may maximize benefits while minimizing potential risks.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Mark R Geier (mgeier@comcast.net) and David A Geier (davidallengeier@comcast.net) are directors of the Institute of Chronic Illnesses, Inc., and CoMeD, Inc. Neither the Institute of Chronic Illnesses, Inc., nor CoMeD, Inc., have any financial interest in the outcome of asthma or exposure to human papillomavirus (HPV) vaccine. Dr Janet K Kern does not hold a management or directorship position at the Institute of Chronic Illnesses, Inc., or CoMeD, Inc.

Ethical approval

Ethical approval was not sought for the present study because the database is a publicly accessible, de-identified database.

Informed consent

Informed consent was not sought for the present study because the database is a publicly accessible, de-identified database.

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