PATTERNS OF USE AND SAFETY OF HUMAN PAPILLOMAVIRUS VACCINES AMONG ADOLESCENTS IN THE UNITED STATES

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ABSTRACT

Nadja Alexandra Vielot: Patterns of Use and Safety of Human Papillomavirus Vaccines among Adolescents in the United States
(Under the direction of Jennifer S. Smith)

Phase III clinical trials and post-licensure surveillance have demonstrated the safety and efficacy of human papillomavirus (HPV) vaccines. The U.S. Advisory Committee on Immunization Practices recommends universal HPV vaccination at age 11-12, alongside tetanus-diphtheria-acellular pertussis (Tdap) and meningococcal conjugate (MenACWY) vaccination.

Despite this recommendation, adolescents initiate HPV vaccination less frequently than Tdap and MenACWY vaccination, due partially to concerns about HPV vaccine safety. Reports of complex regional pain syndrome (CRPS) following HPV vaccination in Japan may have exacerbated safety concerns regarding HPV vaccination. To date, however, no epidemiologic research has linked HPV vaccination to CRPS. We analyzed private U.S. insurance claims between 2006-2014 to assess 1) patterns of use of HPV vaccination compared to Tdap and MenACWY among adolescents; and 2) the hazard of CRPS following HPV vaccination compared to Tdap and MenACWY among girls.

Among 1,691,223 adolescents, HPV vaccination occurred later than Tdap or MenACWY vaccination. Half of vaccinated adolescents received Tdap and MenACWY vaccination only; however, co-administration of all three vaccines increased with birth cohort. Rural adolescents were less likely than urban adolescents to receive each vaccination except in the Northeast, where they were more likely to receive HPV vaccination (incidence rate ratio: 1.09, 95% CI:

1.05, 1.13). Timely HPV vaccination was associated with female sex, urbanicity, Western residence, and later birth cohort.

We identified 563 CRPS cases among 1,232,572 girls. CRPS hazard was not significantly elevated following recent HPV, Tdap, or MenACWY vaccination. Ever receiving Tdap and MenACWY vaccination were associated with CRPS in crude analysis, but were not associated after adjusting for trauma. Concomitant administration of HPV vaccine with other adolescent vaccines conferred no excess hazard of CRPS. Girls with lower limb injuries had the greatest CRPS hazard compared to girls without (HR: 12.4, 95% CI: 10.4, 14.7), and common pediatric illnesses (e.g. asthma, respiratory infections, allergies) were positively associated with CRPS.

HPV vaccination remains suboptimal among U.S. adolescents. We observed no vaccine safety signals with respect to CRPS, supporting current adolescent vaccination recommendations. Health care providers should strongly recommend timely HPV vaccination with other recommended adolescent vaccines to provide optimal protection against HPV-associated cancers.

Dedicated to those who raised me:

Paula Claire Schuman (Mom): If not for you I probably would have majored in psychology and wasted all my smarts. Each day I am grateful for the strength and spirit you gave me, whether you meant to or not. Not one day goes by without missing you.

Jacques Vielot (Dad): You show me love, faith, and support beyond measure. If I can find a man to care for me 1/100th as much as you do, I'll be the luckiest woman alive.

Elizabeth Holt McNaughton (Gramma): I can't believe you took care of us awful children as we grew into even worse teenagers. You should have run for the hills, but I'm glad you didn't. If only you could see Paisley now!

And also to my first, and very best, friends:

Mims: You amaze me with your charm, humor, ambition, beauty, and boundless energy. Thinking of you always makes me smile ☺

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Getting my PhD has been rewarding beyond measure, but let's be honest: I really did it for y'all.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

2vHPV	Bivalent human papillomavirus vaccine
4vHPV	Quadrivalent human papillomavirus vaccine
ACIP	Advisory Committee on Immunization Practices
CDC	Centers for Disease Control and Prevention
CIN2+	Cervical intraepithelial neoplasia, high-grade or more severe
CPT	Current Procedural Terminology
CRPS	Complex regional pain syndrome
EMA	European Medicines Agency
FDA	Food and Drug Administration
HPV	Human papillomavirus
IASP	International Association for the Study of Pain
ICD-9	International Statistical Classification of Diseases and Related Health Problems, 9th Revision
MenACWY	Meningococcal conjugate vaccine
NCD	National Drug Code
SAE	Severe adverse event
Tdap	Tetanus-diphtheria-acellular pertussis vaccine

CHAPTER 1: SPECIFIC AIMS

The World Health Organization (WHO) recommends human papillomavirus (HPV) vaccination due to its strong safety profile and efficacy against cervical precancerous lesions, based on clinical trials and post-licensure surveillance. In the United States (U.S.), prophylactic HPV vaccination is recommended universally to adolescents aged 11 or 12 as part of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) adolescent vaccine platform. However, due in part to safety concerns among adolescents and their parents, HPV vaccine uptake lags behind that of other ACIP-recommended adolescent vaccines, including tetanus-diphtheria-acellular pertussis (Tdap) and meningococcal conjugate (MenACWY) vaccines.

Despite evidence of HPV vaccine safety, over 50 cases of Japanese adolescents with complex regional pain syndrome (CRPS), a nervous system disorder causing pain in the limbs, were reported by the Japanese media to be caused by HPV vaccination. Subsequent media coverage led to public disapproval of HPV vaccination, and the Japanese government withdrew its recommendation for HPV vaccination in June 2013. Uptake of HPV vaccination among eligible adolescents in Japan has since fallen from 80% to <5%, despite the fact that no scientific evidence has demonstrated an association between HPV vaccination and CRPS incidence.

To promote universal uptake of this highly-effective prophylactic vaccine, it is critical to ensure that the benefits of HPV vaccination outweigh the risks. To thoroughly assess HPV vaccination safety, a large sample is needed to detect a sufficient number of vaccinations and

subsequent outcomes for analysis. The current study uses data from MarketScan®, a large employer-sponsored insurance claims database. The specific aims of this study are to:

1) **Describe the patterns of use of HPV vaccination, compared to Tdap and MenACWY vaccination, among adolescents from age 11 in the United States**
    a) Estimate the incidence proportions of HPV vaccination among boys and girls by demographic characteristics, compared to Tdap and MenACWY vaccination.
    b) Compare the characteristics of adolescents vaccinated against HPV, Tdap, and MenACWY.
    c) Describe the most common combinations of adolescent vaccinations received and the incidence rates of concomitant administration of HPV, Tdap, and MenACWY vaccines.
    d) Estimate correlates of timely HPV vaccination at the ACIP-recommended ages.
2) **Estimate the hazard of CRPS following HPV vaccination, compared to Tdap and MenACWY vaccination, among adolescent girls from age 11 in the United States**
    a) Estimate the incidence rate of CRPS among adolescent girls.
    b) Estimate the relative hazard (HR) of CRPS following recent (≤30/90 days) HPV, Tdap, or MenACWY vaccination compared to non-recent (>30/90 days) or no vaccination.
        i) *Hypothesis: CRPS hazard will not be significantly elevated in recently-vaccinated compared to adolescents who were vaccinated in the past or were unvaccinated.*
        ii) We ascertain vaccination status based on CPT codes and estimate hazard ratios (HRs) for the incidence of CRPS within the 30 days or 90 days following vaccination comparing recent vaccination recipients compared to past recipients or non-recipients. We will conduct sensitivity analyses eliminating the time window to assess the hazard of CRPS following recent and non-recent vaccination.

c) Estimate the relative hazard (HR) of CRPS following recent concomitant receipt of adolescent vaccines compared to receipt of single vaccines or reduced combinations of vaccines.
    i) *Hypothesis: CRPS hazard will not be significantly elevated in adolescents recently vaccinated with combinations of vaccines compared to single vaccines or reduced combinations of vaccines, and there will be no excess hazard associated with concomitant vaccination.*
d) Identify other health diagnoses that are positively associated with CRPS incidence based on claims made by girls during follow-up.

The results of this research will provide details on HPV vaccination use and characteristics of vaccinees to aid in targeted vaccination promotion to adolescents and their caregivers. Further, these findings will contribute to the evidence base for HPV vaccine safety, allowing healthcare providers and parents to make informed, evidence-based decisions regarding HPV vaccination in adolescents.

CHAPTER 2: BACKGROUND AND SIGNIFICANCE

Prophylactic human papillomavirus vaccines

Human papillomavirus (HPV) is the most common sexually transmitted infection globally, with over 80% of sexually active adults acquiring HPV at least once during their lives.[1] While most HPV infections resolve on their own within one year, high-risk HPV (hrHPV) types can persist for longer and can develop into invasive cervical carcinoma.[2] Cervical cancer is the fourth most frequent cancer in women globally; in 2012, an estimated 530,000 new cases of cervical cancer occurred, with approximately half of cases resulting in death.[3]

Nearly 100% of cervical cancer cases are caused by hrHPV types, and 70% of cases are caused by hrHPV types 16 and 18. Phase III clinical trials of the prophylactic quadrivalent (4vHPV) and bivalent (2vHPV) HPV vaccines, licensed in the United States by the Food and Drug Administration (FDA) in 2006 and 2009, respectively, demonstrated over 90% efficacy against cervical abnormalities associated with types 16 and 18. The 4vHPV vaccine further demonstrated 90% efficacy against infection with types 6 and 11, which cause approximately 90% of cases of genital warts.[4,5] Clinical trials and post-licensure monitoring have also demonstrated a favorable safety profile of both vaccines, with few or no severe adverse events (SAEs) reported.[5,6] In light of these findings, many countries began integrating HPV vaccination into their national immunization strategies to reduce the burden of HPV infections among young men and women. By November 2016, 87 countries had included HPV vaccination in their national immunization programs, primarily in the Americas, Europe, and the Western Pacific.[7] Recent safety and immunogenicity research also supports the co-administration of HPV vaccines

with other recommended adolescent vaccines, such as tetanus-diphtheria-acellular pertussis (Tdap) and meningococcal conjugate (MenACWY) vaccines, to reduce the burden of clinic visits and improve vaccine uptake and completion of the multi-dose HPV vaccination series.[8]

Varying levels of vaccine coverage among adolescents and young adults have been observed globally, with financial and logistical barriers preventing many individuals from accessing HPV vaccination. However, coverage rates have exceeded 90% in settings where political support and a strong vaccine delivery system are in place.[9] The public health community continually strives to reduce barriers to HPV vaccine uptake, with the goal of vaccinating as many eligible individuals as possible to reduce the incidence of potentially life-threatening cervical cancer.

Patterns of use of HPV and other adolescent vaccines

The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommended routine MenACWY and Tdap vaccination for adolescents beginning at age 11, in 2005 and 2006, respectively.[10–12] Shortly after its FDA approval in 2006, ACIP recommended routine 4vHPV vaccination for girls at age 11 or 12; 2vHPV was recommended for girls at age 11 or 12 following its FDA approval in 2009. On October 21, 2009, ACIP extended the routine 4vHPV vaccination recommendation to 11 and 12-year old boys, marking the first date at which all 11- and 12-year-olds were eligible to receive HPV, Tdap, and MenACWY vaccination. ACIP further recommends that all three vaccines be administered concomitantly (i.e. in the same visit).[13]

Since 2006, the CDC has administered the annual National Immunization Survey – Teen (NIS-Teen) to monitor uptake of adolescent vaccines among adolescents aged 13-17 in the United States.[14] NIS-Teen has consistently demonstrated that HPV coverage rates, or the

proportion of adolescents surveyed who had initiated vaccination, are lower than the coverage rates of Tdap and MenACWY vaccination, despite a wealth of evidence for the safety and efficacy of HPV vaccines.[15] Further, many adolescents do not complete the multi-dose HPV vaccination series and fail to achieve optimal protection against hrHPV infection.[15] Research on HPV vaccination attitudes among adolescents, young adults, and parents of adolescents reveals a distinct distrust of HPV vaccination that is not observed with respect to Tdap and MenACWY vaccination.[16–18] The newness of the HPV vaccine relative to Tdap and MenACWY has contributed to concerns that not enough is known about the vaccine's long-term safety, and fear of SAEs has been a major barrier to uptake and completion of the multi-dose series.[19–21]

Despite sub-optimal uptake, HPV vaccination rates have increased over time with increasing awareness of and recommendation for vaccination. If there are indeed SAEs associated with HPV vaccination, then increasingly more individuals will be at risk for them. Thus, it is critical to provide continued evidence for the safety of HPV vaccines using rigorous scientific methods, and to develop risk mitigation strategies in the event that a link between HPV vaccination and SAEs is established.

Adverse events monitoring following HPV vaccination

A wide variety of local and systemic SAEs have been reported to post-licensure surveillance systems following HPV vaccination, including autoimmune diseases like Guillain-Barre syndrome and central nervous system demyelinating disorders. Many studies using surveillance data and healthcare utilization data have demonstrated that SAEs do not occur more frequently in individuals who receive HPV vaccination relative to those who do not.[22–31] HPV vaccination has been associated with increased risk of syncope (fainting) and anaphylaxis following an injection. However, these events are either considered not serious or rare,

respectively, and the risks of these events are not considered to outweigh the benefits of vaccination.[23,27,30,32,33] HPV vaccines are contraindicated in individuals with sensitivity to yeast (4vHPV) and latex (2vHPV), and vaccine providers are encouraged to monitor patients for 15 minutes following vaccination to prevent injury due to syncope.[34] The World Health Organization (WHO) Global Advisory Committee on Vaccine Safety declared that the HPV vaccines were safe based on post-licensure safety surveillance from the United States and Australia, as well as surveillance conducted by the vaccines' manufacturers.[35]

To date there is no scientific evidence to support the withdrawal of HPV vaccination recommendations based on the vaccines' safety profiles. However, case reports have potentially identified rare SAEs that have not been rigorously evaluated in epidemiological studies. Dedicated studies can evaluate the risks of these SAEs to contribute to the evidence base for HPV vaccine safety.

Complex regional pain syndrome

Complex regional pain syndrome (CRPS) is a disorder of the peripheral nervous system causing chronic pain and discomfort in the limbs. Typical manifestations of CRPS include sensation and pain responses disproportionate to a stimulus (i.e., hyperesthesia and allodynia), dystrophic skin changes (such as reddening and thickening of skin), and changes in sudomotor and vasomotor functions.[36,37] CRPS Types I and II often occur following an injury to the affected limb, such as a fracture or sprain, and share common diagnostic criteria. However, CRPS Type I occurs in the absence of a demonstrable nerve injury, and its pathophysiological mechanism remains unknown. Only two published estimates of CRPS Type I incidence are found in the literature, ranging from 20.57 cases/100,000 person-years over 11 years in Olmstead County, Minnesota, USA, to 26.2/100,000 (95% CI: 23.0, 29.7) person-years over 10 years in The

Netherlands.[38,39] Both estimates were derived from large health records databases, using billing codes to identify CRPS cases and validating cases against medical records or secondary provider review. While apparently rare, CRPS can lead to long-lasting pain, reduced motor function, disability, disruption in daily activities, and reduced quality of life.

Differing CRPS diagnostic criteria complicate research

A CRPS diagnosis is made by ruling out other diseases based on clinical signs and symptoms, and cannot be confirmed with any particular combination of laboratory tests. The International Association for the Study of Pain (IASP) developed diagnostic criteria in 1994, which were highly sensitive for detecting CRPS not had low specificity for ruling out other chronic pain disorders. IASP revised these criteria in 2007 to be more specific; the proposed revisions to the criteria required signs and symptoms to be present at the time of observation.[40] However, both sets of criteria were validated in adult patient populations, and no criteria currently exist to diagnose CRPS in strictly pediatric populations.[40,41] Pediatric CRPS case reports demonstrate that the clinical manifestation of CRPS differs from that in adult cases, and the diagnostic criteria developed for adults might be inappropriate for diagnosing pediatric cases.

In contrast to adult cases, pediatric CRPS manifests primarily in girls, is more likely to involve a lower limb, less often involves neurological dysfunction, and more often involves psychological distress.[42,43] Pediatric CRPS case reports often describe patients as having a history of psychological trauma or unstable familial relationships or home environments.[44–62] CRPS is often treated with a combination of analgesics and/or nerve blockers, physical therapy in the affected limb(s), and psychotherapy.[43,61–64] The prognosis for children is typically more favorable than for adults, with a lower proportion of children experiencing long-term disability or dysfunction. In some cases, CRPS symptoms in children have resolved on their own without

intervention.[65] In a study of CRPS patient outcomes following intense physical therapy, secondary episodes of pain occurred in one-third of patients, usually within six months of resolution of the initial episode. However, pain subsided following reinstatement of the physical therapy program.[62]

HPV vaccination and CRPS in Japan

In March 2013, local press in Japan reported on 50 cases of adolescent girls suffering from CRPS after receiving HPV vaccination.[66] The CRPS patients and their families created advocacy groups critical of the government and demanded compensation for their injuries, but were largely denied on the basis that the vaccine was not part of the National Immunization Programme (NIP). One month later, in April 2013, HPV vaccination was integrated into the NIP; however, following pressure from victims' groups, the Ministry of Health, Labor, and Welfare (MHLW) rescinded its recommendation for HPV vaccination in June 2013. By that time, over 8 million individuals were estimated to have received the vaccine in Japan.[67] A subsequent case series documented 40 young women reporting to a Japanese hospital, having received 2vHPV or 4vHPV vaccination prior to onset of symptoms.[68] These cases were diagnosed according to the historical IASP criteria with lower specificity, and may have been over-diagnosed in some cases. The report also failed to account for the prior trauma history of suspected CRPS cases, neglecting an important etiological component of CRPS development.

Despite the weak evidence for an association between HPV vaccination and CRPS, the patients and their families used social media to promulgate anti-vaccine sentiment. Due to the wide reach of social media channels, fear and suspicion of HPV vaccines has the potential to spread rapidly across countries and regions. Further, the readiness of the Japanese government to rescind the recommendation for HPV vaccination likely validated public misconceptions of HPV

vaccine safety, even though this action was not based on scientific evidence. To date, no epidemiological studies have been conducted to rigorously measure the association between vaccination and CRPS incidence. A 2015 review by the European Medicines Agency (EMA) of the evidence from clinical trials and post-licensure surveillance concluded that HPV vaccination was not associated with elevated risk of CRPS or postural orthostatic tachycardia syndrome (POTS), which was also observed in some of the Japanese cases.[69,70] Despite the lack of evidence for an association with CRPS, HPV vaccine uptake in Japan fell from nearly 80% to less than 5% by the end of 2014.[71] If other countries follow suit based solely on public opinion, this potentially life-saving vaccine might fail to reach the populations at greatest risk for HPV infection.

Hypothesized pathways for vaccine-induced CRPS

The most commonly-identified causes of CRPS include a history of trauma to the limb or surrounding areas, including fractures, sprains, and surgeries.[42,43,45,47–50,64,70,72–75] A pathophysiological mechanism for vaccine-induced CRPS has not been identified, but several hypotheses have been proposed. One hypothesis is that the needle itself inflicts damage on nerves at or near the injection site and incites excessive pain in individuals with underlying autonomic dysfunction; another is that injection-induced pain can cause the patient to immobilize or hold the affected arm in an unusual position, contributing to loss of function and continued pain.[76–78] Following the review by the EMA, the researchers noted that "preceding viral illness" has been associated with CRPS development, much like injuries.[69] The immune inflammatory response following vaccination could be such a trigger in recipients of HPV or other commonly administered vaccines. Indeed, several case reports have described CRPS development in adolescents following influenza, hepatitis B, diphtheria-tetanus, and rubella vaccination.[44,65,79,80]

Gaps in the literature

HPV vaccination relative to Tdap and MenACWY vaccination has been studied annually through NIS-Teen since 2006. However, NIS-Teen has not assessed the influence of residential factors on vaccination patterns, or patterns of vaccine co-administration. Urbanicity has been a strong predictor of adolescent vaccination, but differences in urbanicity by region have not been assessed in the literature. Identifying areas with sub-optimal vaccination can help develop targeted pro-vaccination policies to ensure high coverage of these important vaccines. Co-administration is important to ensure receipt of all adolescent vaccines, and with the increased uptake of HPV vaccination over time we would expect to see concomitant increases in co-administration. Further, if there is a mechanism for vaccine-induced CRPS related to the number or combination of vaccines administered, it is necessary to understand these co-administration patterns from an objective data source so they can be assessed as risk factors for SAEs.

The decision by the Japanese government to withdraw the recommendation for HPV vaccination was premature given that little is known about its association with CRPS incidence. CRPS is a rare disease, and it is difficult to conduct research in large enough samples of cases that would yield generalizable study findings. The literature is comprised primarily of case reports or case series from health care facilities reporting on small numbers of CRPS patients. [44–48,50–53,55,57–59,65,72,73,77,79–92] Very few reports exist of cases following vaccination, and none of these assess a causal relationship between vaccination and CRPS using epidemiological methods.[44,65,77,79,80] Facility-based studies with long study periods have managed to reach sample sizes of several hundreds and over 1,000 in one case, but these studies were largely descriptive and did not assess vaccination as a potential causal risk factor for CRPS.[93–95]

Large healthcare databases are useful tools to assess the use and safety of vaccines in large, diverse populations.

Healthcare utilization databases, including electronic medical records and insurance claims databases, are increasingly used to study real-world use of pharmaceuticals, including vaccines. In the United States, NIS-Teen has been the primary tool for assessing uptake of HPV, Tdap, and MenACWY vaccination, and the Vaccine Adverse Events Reporting System (VAERS) and administrative data from managed care organizations have estimated the risks of SAEs following vaccination. However, NIS-Teen relies on random digit dialing to identify study participants, which may result in selection bias. Errors in parental recall of their children's vaccination histories or providers' medical records may lead to misclassification of vaccination status. VAERS is a passive surveillance system that is subject to underreporting of SAEs. Insurance claims data reduce these ascertainment errors by providing comprehensive and objective data on receipt of medical services, including specific medical procedures and diagnoses. Additionally, none of the previously-used databases has provided a sample size large enough to detect rare outcomes such as CRPS. Using large healthcare utilization databases can increase the sample size of CRPS cases by searching a large number of providers, facilities, and geographic areas. This type of data has never before been used to assess CRPS risk factors.

CHAPTER 3: METHODS

Data source

The MarketScan® Commercial Claims and Encounters database, owned and maintained by Truven Health Analytics™, contains insurance claims of over 170 million unique enrollees from US-based healthcare facilities since 1995.[96] MarketScan provides a large, diverse, and representative sample of enrollees in employer-sponsored health insurance plans. The database provides unique enrollee ID numbers in lieu of names, and patient location information is restricted to broad geographic areas to protect patient confidentiality. The data are maintained on a secure server administered by the UNC Cecil G. Sheps Center for Health Services Research, which is password-protected and accessible only to persons authorized by Truven Health Analytics to access the data.

MarketScan provides insurance claims in a variety of tables, including insurance plan enrollment details, claims for inpatient and outpatient medical services, and claims for prescription medication fills. Medical services claims are coded using International Statistical Classification of Diseases, Ninth Revision (ICD-9) codes to reflect the relevant diagnoses at the time of the encounter; Current Procedural Terminology (CPT) codes to reflect the medical procedures administered at the time of the encounter; and National Drug Codes (NDC) to identify prescription medications that were filled and billed to the enrollee's insurance plan. We used MarketScan insurance claims to describe the patterns of use of HPV, Tdap, and MenACWY vaccines, and to estimate the incidence of CRPS and the hazard ratio (HR) for CRPS comparing adolescents who recently received HPV vaccination to those who did not. We used CPT codes to

ascertain exposures to HPV, Tdap, and MenACWY vaccination, ICD-9 codes to identify CRPS cases, and CPT, ICD-9, and NDC codes to indicate other health history variables of interest for the analyses described herein.

Study population

All MarketScan enrollees are beneficiaries of employer-sponsored insurance plans, and adolescents are typically the children or other dependents of the primary beneficiaries. All enrollees are residents of the 50 United States, the District of Columbia, and Puerto Rico.

We created open cohorts of 11-year-old enrollees for each research aim, based on the ACIP recommendations for HPV, Tdap, and MenACWY vaccination in adolescents from 11 years of age. Specific Aim 1 included boys and girls, while Specific Aim 2 included girls only. We followed adolescents from their 11th birthdays, the earliest opportunity to receive adolescent vaccination per ACIP recommendations, to maximize the probability of capturing vaccination initiation. Adolescents who received HPV, Tdap, or MenACWY vaccination prior to age 11 were eliminated from the final study sample. Because date of birth is protected health information, we searched monthly insurance enrollment files to identify the month in which the adolescent's age changed, and then set the date of birth to the last day of that month. Some enrollees have more than one period of continuous insurance plan enrollment due to temporary loss or change of insurance coverage. The observation period for these enrollees was restricted to the enrollment period during which they turned 11, to avoid under-ascertainment of vaccination or CRPS diagnoses that may have occurred outside of the insurance billing system.

Analytic methods

Specific Aim 1: Patterns of use of HPV, Tdap, and MenACWY vaccines

The study period began October 21, 2009 – when ACIP supported HPV vaccination for boys – marking the first opportunity for all eligible adolescents to receive all three recommended vaccines. We included girls and boys who 1) turned 11 years of age between 2009 and 2014; 2) had no prior history of adolescent vaccination; and 3) had at least one year of continuous insurance plan enrollment prior to the start of follow-up.

We searched outpatient services claims for the first billed claim for 2vHPV (CPT code 90650) or 4vHPV (CPT code 90649), Tdap (CPT code 90715, ICD-9 code 9939), or MenACWY (CPT code 90734). We excluded Tdap claims related to injuries or accidents (ICD-9 codes 037.X, 87X-91X, V01-V02, all E codes) or receipt of antenatal care (ICD-9 codes V22.X-V39.X), as these instances do not reflect routine Tdap vaccination. While HPV vaccination requires multiple doses and MenACWY vaccine requires a booster, limited follow-up times might prevent us from observing all recommended doses of these vaccines. Thus, we focused our analyses on initiation of these vaccines rather than completion of the series.

We followed adolescents until the end of their enrollment period or December 31, 2014, the last date for which claims data were available. Outcomes of primary interest included uptake proportions for each vaccine, the prevalence of different vaccination combinations, incidence rates of vaccine co-administration over time, and timeliness of HPV vaccination. The time to vaccination for HPV, Tdap, and MenACWY was estimated as the difference between the 11th birthday and the date of the first vaccination. We used generalized estimating equations with a Poisson distribution and a robust variance estimator to estimate incidence rate ratios (IRR) and 95% confidence intervals (CI) for correlates of vaccination, and incidence rates (IR) of vaccine co-administration over time. Descriptive statistics summarized service-related characteristics at

the time of vaccination, and receipt of multiple and co-administered vaccines. We plotted the cumulative incidence of receiving the first dose of HPV vaccine at age 11 or 12 (i.e. timely HPV vaccination). Incidence rates and cumulative incidence of vaccination were stratified by covariates of interest, including sex; region (Northeast, North Central, South, West); urbanicity, as defined by urban residence (metropolitan statistical area with population ≥50,000) or rural residence (micropolitan statistical area with population <50,000); and insurance plan type.

As many as 18 states have offered at least one adolescent vaccine free of charge, regardless of income level, since 2006 (Alaska, Connecticut, Hawaii, Idaho, Massachusetts, Maine, Nevada, New Hampshire, New Mexico, North Carolina, North Dakota, Oregon, Rhode Island, South Dakota, Vermont, Washington, Wisconsin, and Wyoming).[97] Adolescents from these states may have received vaccines without filing insurance claims, and thus their vaccination status would not be ascertained from MarketScan data. We conducted a sensitivity analysis excluding these states to assess potential bias due to under-ascertainment of vaccination status.

Specific Aim 2: Hazard of CRPS following recent HPV, Tdap, or MenACWY vaccination

To test our Aim 2 hypothesis, we estimated that we would require a sample size of approximately 250,000 to achieve 80% power to identify a 100% increased hazard of CRPS in vaccinated adolescents (i.e. HR=2.0), assuming the lowest incidence rate reported in the literature (20.57 cases/100,000 person-years).

The study period began June 29, 2006 – the date of the ACIP recommendation for HPV vaccination in girls – and ended December 31, 2014. We included girls who 1) turned 11 years of age between 2006 and 2014; 2) had no prior claims for adolescent vaccination or CRPS; and 3) had at least one year of continuous insurance plan enrollment prior to the 11th birthday. We

observed girls from the 11th birthday until the date of a claim for a CRPS diagnosis, or censorship at disenrollment from their insurance plan or December 31, 2014. For girls with multiple continuous enrollment periods, we restricted observation to the enrollment period that included the 11th birthday. Because date of birth is protected health information, we searched monthly insurance enrollment files to identify the month in which the adolescent's age changed, and then set the date of birth to the last day of that month.

The primary exposures were receipt of 2vHPV(CPT code 90650) or 4vHPV (CPT code 90649), Tdap (CPT code 90715, ICD-9 code 9939), or MenACWY (CPT code 90734) vaccination, or concomitant Tdap+MenACWY. Secondary exposures included co-administration of HPV vaccine with one or more of Tdap, MenACWY, or influenza (CPT codes 4037F, 90658-90688, 90724, 90737) vaccines, and the co-administration of HPV vaccine with Tdap+MenACWY. By identifying multiple exposure patterns we were able to assess 1) the individual associations of each vaccine with CRPS, and 2) any additional influence of co-administration or specific co-administered combinations on the association between adolescent vaccination and CRPS incidence.

The primary outcome was a diagnosis of CRPS, based the International Disease Classification of Diseases, Ninth Revision (ICD-9) codes for reflex sympathetic dystrophy (ICD-9 codes 337.2, 337.2X) and algoneurodystrophy or Sudeck's atrophy (ICD-9 code 733.7). We also identified cases of possible CRPS, based on ICD-9 codes for other idiopathic peripheral autonomic neuropathies (ICD-9 codes 337, 337.0, 337.00, 337.09, 337.1, 337.9) and neuralgia (ICD-9 code 729.2). Sensitivity analyses used a composite outcome of CRPS and possible CRPS cases.

We used causal diagrams to identify covariates of interest that are associated with adolescent vaccination and a CRPS diagnosis. We conditioned on female sex, insured status, and age in the study design, by restricting to insured girls at age 11. Covariates to include in our analyses included a history of physical trauma in the year prior to follow-up or diagnosis of physical trauma over the course of follow-up, as physical trauma is the strongest known risk factor for CRPS.[48,50,64,98,99] Physical trauma was ascertained using ICD-9 codes for fractures, dislocations, sprains, motor vehicle accidents, and CPT codes for setting of fractures and dislocations and surgeries involving the musculoskeletal or nervous systems (Appendix 1).

We first estimated the incidence rate and 95% confidence interval (CI) for CRPS using generalized estimating equations with a Poisson distribution and a robust variance estimator. Next, we assessed the associations of adolescent vaccinations with incident CRPS using time-dependent Cox models to estimate hazard ratios (HR) and 95% CIs, comparing the hazard of CRPS between recently-vaccinated and previously-vaccinated or unvaccinated girls. We estimated crude HRs and trauma-adjusted HRs.

Vaccination and trauma were considered time-dependent covariates. All girls were unexposed to all vaccinations at the beginning of follow-up. Girls who never received vaccination remained unexposed for the full follow-up period, while girls who received vaccination became exposed at the first date of a claim for vaccination. To assess the association of recent vaccination with CRPS, we considered girls exposed for 30 and 90 days after vaccination. At the end of the exposure window, vaccination status returned to unexposed. In the case of multiple doses of HPV vaccine, vaccination status returned to exposed after a subsequent dose was received, and remained exposed until the end of the exposure window. In a sensitivity analysis, we eliminated the exposure window to assess the hazard of CRPS following any recent

or non-recent vaccination; girls with claims for vaccination were considered exposed from the first date of vaccination and for the duration of follow-up. Trauma status was ascertained in a similar fashion. Girls with no claims for trauma remained unexposed for the duration of follow-up, whereas girls with claims for trauma were considered exposed from the date of the claim and for the duration of follow-up.

Next, we used time-dependent Cox models including interaction terms between vaccinations to assess the hazard of CRPS following receipt of 1) concomitant HPV vaccination versus HPV vaccination alone; and 2) concomitant Tdap+MenACWY+HPV versus Tdap+MenACWY. We estimated crude and trauma-adjusted HRs, and p-values to test the statistical significance of the vaccination interactions.

Finally, we identified additional diagnoses from girls' claims records that were positively associated with CRPS incidence. We identified the 400 most prevalent diagnoses among girls in the sample between the 11^{th} birthday and the end of follow-up at CRPS diagnosis or censorship. We then created binary variables indicating whether or not each girl had the diagnosis. All diagnoses were considered time-dependent covariates using the method described above: girls without the diagnosis remained unexposed for the duration of follow-up, and girls with the diagnosis were considered exposed from the date of the diagnosis claim and for the duration of follow-up. We used time-dependent Cox models to estimate bivariate HRs for the association between each diagnosis and CRPS incidence; similar diagnoses were combined into a composite variable, and new HRs using the composite variable were estimated.

CHAPTER 4. PATTERNS OF USE OF HUMAN PAPILLOMAVIRUS AND OTHER ADOLESCENT VACCINES IN THE UNITED STATES

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommended routine meningococcal conjugate (MenACWY) and tetanus-diphtheria-acellular pertussis (Tdap) vaccination for adolescents at age 11, in 2005 and 2006, respectively.[10–12] ACIP subsequently recommended routine human papillomavirus (HPV) vaccination for females aged 11-12 on June 29, 2006, and for males aged 11-12 on October 21, 2009.[100–102] Phase III clinical trials of the prophylactic quadrivalent (4vHPV) and bivalent (2vHPV) HPV vaccines demonstrated over 90% efficacy against high-grade or greater cervical intraepithelial neoplasia (CIN-2+) associated with high-risk HPV (hrHPV) types 16 and 18.[4,103] Despite ACIP's recommendations and strong evidence for the safety and efficacy of HPV vaccines, receipt of at least one dose of HPV vaccine (56.1%) among boys and girls aged 13-17 lags behind receipt of Tdap (86.4%) or MenACWY (81.3%) vaccines in the United States, according to the 2016 nationally-representative National Immunization Survey-Teen (NIS-Teen).[15]

In the NIS-Teen surveys, parents report their children's vaccination status and their children's vaccination providers are contacted to confirm vaccination status. However, vaccination status might be misclassified if parents do not accurately recall their children's vaccination providers, or if providers have inaccurate vaccination records.[104] Further, the random digit dialing sampling strategy used for NIS-Teen results in low response rates, and the sample may not be generalizable to the U.S. population. Alternatively, insurance claims provide accurate

data on adolescent vaccination for millions of individuals, eliminating the need to review medical records and reducing recall and information biases. Further, insurance claims also allow monitoring of co-administration of vaccines on the same service date and trends over time in uptake of different vaccine combinations, which have only been recently reported in two studies using NIS-Teen data.[105,106]

Here we present data from employer-sponsored insurance claims to describe patterns of use of HPV, Tdap, and MenACWY vaccination among vaccine-eligible girls and boys in the United States. Results from this study will identify gaps in vaccination coverage and can inform targeted adolescent vaccination promotion strategies.

Methods

Study population

The MarketScan® Commercial Claims and Encounters database captures patient-level medical claims provided by over 300 large employers in all 50 states, the District of Columbia, and Puerto Rico, including over 170 million unique enrollees since 1995.[107] MarketScan provides patient demographic data, type and duration of health plan enrollment, claims for medical diagnoses and procedures using International Classification of Disease – 9th Revision (ICD-9) and Current Procedural Terminology (CPT) codes, respectively, and dates of medical services. We obtained MarketScan data between 2000 and 2014 from Truven Health Analytics.

The study period began October 21, 2009 – when ACIP supported HPV vaccination for boys – marking the first opportunity for all eligible adolescents to receive all three recommended vaccines. We included girls and boys who 1) turned 11 years of age between 2009 and 2014; 2) had no prior history of adolescent vaccination; and 3) had at least one year of continuous insurance plan enrollment prior to the start of follow-up.

Data analysis

We began observing adolescents from their 11th birthdays, when they became eligible for adolescent vaccination according to the ACIP recommendations. Because date of birth is protected health information, we searched monthly insurance enrollment files to identify the month in which the adolescent's age changed, and then set the date of birth to the last day of that month. We followed adolescents from their estimated 11th birthdays (Time 0) until vaccination, disenrollment, or the end of the study period on December 31, 2014.

We searched outpatient records for the first billed claim for 2vHPV (CPT code 90650) or 4vHPV (CPT code 90649), Tdap (CPT code 90715, ICD-9 code 9939), and MenACWY (CPT code 90734). We excluded Tdap claims related to injuries or accidents (ICD-9 codes 037.X, 87X-91X, V01-V02, all E codes) or receipt of antenatal care (ICD-9 codes V22.X-V39.X). While the HPV vaccination series includes multiple doses and MenACWY vaccine requires a booster, we only identified the first dose of each vaccine, as limited follow-up might prevent us from observing subsequent doses. Descriptive statistics summarized service-related characteristics at the time of vaccination, and the combinations of vaccines received by adolescents, including co-administered vaccines.

For each vaccine, we estimated time to vaccination as the difference between Time 0 and the date of the first vaccination claim. We estimated total follow-up time as the difference between Time 0 and the date of service for adolescents who received vaccination; or the difference between Time 0 and the date of disenrollment or the end of the study period for adolescents who did not receive vaccination. We used generalized estimating equations with a Poisson distribution and a robust variance estimator to estimate vaccination incidence rates (IR) per 10,000 person-months of observation, incidence rate ratios (IRR) and 95% confidence

intervals (CI) for correlates of vaccination, and IRs of vaccine co-administration over time. Incidence rates and cumulative incidence were stratified by covariates of interest, including sex; region (Northeast, North Central, South, West, per the U.S. Census Bureau[108]); urbanicity, as defined by urban residence (metropolitan statistical area with population ≥50,000) or rural residence (micropolitan statistical area with population <50,000); receipt of primary care in the year prior to observation; and insurance plan type. We also plotted the cumulative incidence of receiving the first dose of HPV vaccine at age 11 or 12 (i.e. timely HPV vaccination), stratified by sex, urbanicity, region, and birth cohort.

As many as 18 states had offered at least one adolescent vaccine free of charge, regardless of income level, since 2006 (Alaska, Connecticut, Hawaii, Idaho, Massachusetts, Maine, Nevada, New Hampshire, New Mexico, North Carolina, North Dakota, Oregon, Rhode Island, South Dakota, Vermont, Washington, Wisconsin, and Wyoming).[97] Adolescents from these states may have received vaccination without filing insurance claims, and thus their vaccination status would not be ascertained from MarketScan data. We conducted a sensitivity analysis excluding these states to assess potential bias due to under-ascertainment of vaccination status.

Analyses were performed in SAS 9.3 (Cary, North Carolina). Proportional Venn diagrams were created using the eulerAPE application (Canterbury, UK).[109] The University of North Carolina Office of Human Research Ethics approved this study.

Results

The analytic cohort included 1,691,223 adolescents: 822,544 girls and 868,669 boys. The median duration of follow-up was 16 months (interquartile range, 7-31 months) (Table 4.1). We observed at least one adolescent vaccination for 948,995 adolescents (56.1%) during the

observation period. Of the 922,137 adolescents who were enrolled until the end of the study period on December 31, 2014, 66.7% of them received any adolescent vaccination; of the 769,086 adolescents who disenrolled during follow-up, 43.4% of them received any adolescent vaccination. Similar percentages of girls and boys received Tdap and MenACWY; however, the proportion of adolescents receiving HPV vaccination was higher in girls than boys (21.9% vs. 15.1%) (Table 4.1). Mean age at receipt of the first dose of HPV vaccine (11.8 years) was higher than that for Tdap and MenACWY (11.2 years for both), and girls received HPV vaccination relatively earlier than boys (mean age 11.7 years vs. 12.0 years). Among adolescents who received any vaccination, over 96% received Tdap or MenACWY vaccination within the ACIP-recommended age range. In contrast, 81% of girls and 72% of boys received HPV vaccination within the ACIP-recommended age range (Table 4.2).

One-quarter of adolescents who received any vaccination received all three recommended vaccines; 50.6% received Tdap and MenACWY only (Figure 4.1). For adolescents who received Tdap and MenACWY vaccination only, 92.3% received both concomitantly at their initial adolescent vaccination visit. However, only 24.1% of adolescents who received all three vaccinations received them concomitantly at the initial vaccination visit. Co-administration IRs of Tdap+MenACWY were higher than those for HPV+Tdap+MenACWY in each birth cohort, though IRs of both co-administration combinations increased steadily with each successive birth cohort (Figure 4.2).

The IRs of HPV, Tdap, and MenACWY vaccination were lower in rural adolescents than urban adolescents (Table 4.3). The highest HPV vaccination IRs were observed in the West (117.2 95% CI: 116.3, 118.0), and the lowest HPV vaccination IRs were observed in the South (91.3, 95% CI: 90.8, 91.9). The West region had the lowest IRs of Tdap (IR: 404.7, 95% CI:

404.2, 407.1) and MenACWY (IR: 299.7, 95% CI: 297.8, 301.5) vaccination. The IRs of all vaccinations were lowest among adolescents with comprehensive insurance plans, and adolescents who had received any primary care in the year prior to the start of observation had higher IRs of all vaccinations than those without a primary care visit (Table 4.3).

Overall, rural adolescents had lower IRs than urban adolescents of HPV (IRR: 0.76, 95% CI: 0.75, 0.77), Tdap (IRR: 0.58, 95% CI: 0.57, 0.58), and MenACWY vaccination (IRR: 0.53, 95% CI: 0.53, 0.54) (Table 4.4). Rural adolescents in the North Central, South, and West regions were less likely than urban adolescents to receive HPV vaccination, whereas adolescents in the Northeast were more likely to receive HPV vaccination (IRR: 1.09, 95% CI: 1.05, 1.13) (Table 4.4).

The cumulative incidence of timely HPV vaccination differed across subgroups (Figure 4.3). Timely HPV vaccination was more frequent in girls versus boys, regardless of the time since start of follow-up. Adolescents residing in urban areas had a higher incidence of timely vaccination than adolescents residing in rural areas, and adolescents in the West had higher incidence of timely HPV vaccination than adolescents in the Northeast, North Central, or South regions. With more recent birth cohort, the cumulative incidence of timely HPV vaccination increased incrementally (Figure 4.3).

After repeating these analysis excluding the 18 states that offered free universal adolescent vaccine coverage, we observed comparable vaccination proportions, vaccination combinations, and stratified IRs of vaccination. None of the interpretations of our findings were changed.

Discussion

Among 1.7 million vaccine-eligible adolescents with employer-sponsored insurance in the United States, we observed relatively lower IRs of HPV vaccination than Tdap or MenACWY vaccination in girls and boys. Further, HPV vaccination was more often delayed beyond the 11-12-year age range universally recommended by ACIP compared to Tdap and MenACWY vaccination. For all three recommended vaccines, rural adolescent residents were consistently less likely to be vaccinated than their urban counterparts in all geographical regions (South, Northeast, West) except in the Northeast. Our also data suggest birth cohort effects for co-administration of all three recommended vaccines, suggesting increased use of co-administration over time and increased integration of HPV into the adolescent vaccination package over time.

Similar to other studies, our data indicate that adolescents have frequent missed opportunities for HPV vaccination, namely clinic visits in which Tdap and/or MenACWY vaccines were administered.[110] In our sample, though over half of adolescents had initiated adolescent vaccination, most adolescents had not received HPV vaccination by the end of follow-up. Of those who did, 23% received HPV vaccination outside of the ACIP-recommended age range (Table A1). The National Health and Nutrition Examination Survey found that 43% of adolescents initiated HPV vaccination after or in the same year as sexual debut, increasing their risk for pre-vaccination HPV exposure.[111] While ACIP recommends catch-up vaccination for adolescents older than 12, HPV vaccine effectiveness is highest prior to sexual debut.[34] Among 1,139 inner-city adolescent women in New York City, receiving HPV vaccination after age 15 was associated with an increased hazard of high-grade cervical lesions relative to receiving vaccination prior to age 15.[112] Thus, it is critical that providers recommend HPV vaccination in

boys and girls at the earliest opportunity, including sick visits and visits for other adolescent vaccinations.

Our study found that rural adolescents in the Northeast had higher IRs of HPV vaccination than their urban counterparts, though rural adolescents overall had lower IRs of vaccination with all three adolescent vaccines. The increase in HPV vaccination that we observed in rural, Northeastern adolescents could simply be a function of the smaller size of this region and fewer access barriers to vaccination for rural adolescents. Future research should identify specific barriers to vaccination in rural areas, besides economic factors, and differences in these factors by region. Provider factors in rural areas may influence whether they recommend HPV vaccination for their adolescent patients.[113] A study comparing HPV vaccination recommendation behavior among 334 pediatricians in Appalachian and non-Appalachian counties of Kentucky and West Virginia found that Appalachian pediatricians were less likely to recommend HPV vaccination to their adolescent patients.[114] Further, rural adolescents are more likely to receive care form a family physician rather than a pediatrician, and thus may be less likely to receive recommendations for HPV vaccination.[115] All provider types who treat adolescents are encouraged to use CDC-developed messages to recommend HPV vaccination to eligible adolescents. In a national sample, CDC messages pertaining to the high prevalence of HPV infection, the importance of HPV vaccination for cancer prevention, and the efficacy of HPV vaccination were acceptable to caregivers who were reticent to vaccinate their adolescents.[116]

Studies of caregivers' attitudes toward HPV vaccination reveal concerns about vaccine safety and effectiveness, low perception of risk for HPV infection, and unwillingness to vaccinate adolescents who presumably are not sexually active against a sexually transmitted

infection.[117–119] Adolescent health care providers should actively communicate the evidence-based vaccination benefits to caregivers, particularly in regions that have low HPV vaccination coverage. Additionally, enhancing healthcare practices to facilitate vaccination can effectively increase HPV vaccination initiation. In a cluster randomized trial in Pennsylvania pediatric and family medicine practices, The 4 Pillars™ Practice Transformation Program, which promotes strategies such as patient notification for vaccination and establishing HPV vaccination champions in practices, was associated with greater increases in HPV vaccination initiation compared to control practices.[120]

Our primary limitation is the short follow-up time (median 16 months) to observe vaccination receipt, preventing us from observing vaccination events that occurred after the end of follow-up. As a result, our longitudinal study yielded smaller vaccination incidence proportions than the vaccination coverage rates reported by NIS-Teen, which used cross-sectional methods. We were also limited to reporting only the first instance of HPV and MenACWY vaccination to avoid drawing invalid conclusions about completion of these vaccination series. Second, there is a chance of misclassification of vaccination status due to the use of incorrect or alternate CPT or ICD-9 codes. We attempted to use all relevant vaccination codes to minimize under-ascertainment of vaccination receipt. However, MarketScan is not able to track all enrollees who switch between insurance plans, and thus historical vaccination data for adolescents who changed insurance might not be recognized. Third, because MarketScan represents employer-sponsored insurance claims, our results may not be generalizable to Medicaid and uninsured populations. We also are unaware of how many MarketScan enrollees are Medicaid-eligible, and might receive vaccination through channels that bill Medicaid. However, we observed comparable vaccination proportions and IRs after excluding states that

offer free adolescent vaccination, indicating that vaccination patterns are similar between adolescents with access to free vaccination and those without. These analyses should be replicated in Medicaid data to identify any disparities in vaccination patterns by insurance source. The Affordable Care Act of 2010 guarantees that immunizations are covered under all insurance plans.[121] Deductible and other payment factors or provider selection factors, however, may influence vaccination decisions. Future research should assess the impacts of insurance coverage on adolescent vaccination. Finally, MarketScan lacks data on race and ethnicity, and we cannot know the degree to which regional differences are influenced by racial or ethnic variation in vaccination patterns.

Strengths of this analysis include a large sample of adolescents in the United States and minimally-biased documentation of vaccine receipt. In identifying nearly one million vaccinated adolescents, we had sufficient power to identify correlates of vaccination status with precision. Using procedure and diagnosis codes from a large insurance claims database, we estimated vaccination IRs beginning at the age recommended by ACIP, allowing us to assess vaccination timeliness. We also made robust estimates of vaccination incidence using methods that account for differential follow-up times and censoring.

Recent changes to HPV vaccine availability and recommendations may improve the uptake and impact of this vaccine. A 9-valent vaccine (9vHPV) preventing the seven hrHPV types most highly-associated with CIN2+ was approved by the FDA in December 2014, and recommended by ACIP for 11- and 12-year-olds in March 2015.[122,123] This broad-coverage prophylactic vaccine promises to prevent even more cases of CIN-2+ attributed to hrHPV types when administered in a timely fashion. Future research can use MarketScan to monitor patterns of use of 9vHPV relative to 4vHPV and 2vHPV, and its concomitant use with Tdap and

MenACWY. Additionally, following a review of immunogenicity and effectiveness data, ACIP recommended in December 2016 that the HPV vaccination series be reduced to two doses from three for adolescents who vaccinate before age 15.[124] This new recommendation may increase the acceptability of HPV vaccination due to a lower burden of clinic visits; reduce safety concerns associated with multiple doses of HPV vaccination; and simplify medical record-keeping and vaccination status monitoring.

Conclusions

Offering HPV, Tdap, and MenACWY as a comprehensive adolescent vaccination platform could increase HPV vaccination to the same levels as Tdap and MenACWY. Safety and immunogenicity research supports co-administration of HPV, Tdap, and MenACWY, and ACIP recommends co-administration of all three vaccines at age 11 or 12.[125,126] HPV vaccination trends are encouraging, as indicated by more timely HPV vaccination and co-administration of all three recommended adolescent vaccines among adolescents born more recently. However, adherence to ACIP recommendations for HPV vaccination timing and HPV vaccination in boys remains particularly sub-optimal. Providers can educate caregivers about the benefits of vaccination, including information about recent disease outbreaks due to poor vaccine coverage. Providers should also avoid creating exceptions for HPV vaccination, stressing that all adolescent vaccines are safe, effective, and appropriate for 11- and 12-year-old girls and boys, unless contraindicated. Demand for and access to HPV vaccination for adolescents in rural areas must be improved. Early and concomitant vaccination can reduce the burden of adolescent preventive care in harder-to-reach areas.

CHAPTER 5: HAZARD OF COMPLEX REGIONAL PAIN SYNDROME FOLLOWING HPV AND OTHER ADOLESCENT VACCINATION

Introduction

In the United States, the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommends universal HPV vaccination to girls and boys aged 11 or 12 as part of the adolescent vaccine platform, alongside tetanus-diphtheria-acellular pertussis (Tdap) and meningococcal conjugate (MenACWY) vaccination.[13] Phase III clinical trials and post-licensure surveillance have demonstrated the safety of all three adolescent vaccines, with no conclusive evidence for severe adverse events (SAE) following vaccination.[4,5,22,127–130] Syncope and anaphylaxis have been associated with HPV vaccination, though these events are considered non-severe and rare, respectively.[27,32,131] Suspected vaccine-attributable SAE continue to be investigated, often following a safety signal from a case report or surveillance data.

In 2013, Japanese media reported on 50 cases of girls experiencing symptoms of complex regional pain syndrome (CRPS) following HPV vaccination. Complex regional pain syndrome – formerly known as reflex sympathetic dystrophy, Subdeck's atrophy, or algoneurodystrophy – is a rare disorder of the autonomic nervous system that causes pain and sudomotor, vasomotor, and trophic changes in the limbs.[42] Onset of CRPS commonly follows trauma to the affected limb, such as a sprain or fracture, and less commonly follows an infection.[42,43,45,47–50,64,70,72–75] The published literature contains two estimates of CRPS incidence, ranging from 20.6 cases/100,000 person-years over 11 years in Olmstead County, Minnesota, USA, to 26.2/100,000 person-years over 10 years in The Netherlands.[38,39] Pediatric CRPS (ages 5-17) primarily affects girls (~80%

of cases), predominantly affects a lower limb, often presents with comorbid mental illness or psychological distress, and is less likely than adult CRPS to follow a traumatic event.[42,43,45,48,52,61,132–134]

CRPS is classified into two types, which share common diagnostic criteria but differ in their etiology. Unlike CRPS Type II, CRPS Type I cases do not present with demonstrable nerve damage, and thus Type I cases are more commonly linked to non-injurious events.[37] Several case reports have described CRPS Type I (hereafter CRPS) cases following tetanus, influenza, rubella, and hepatitis B vaccination.[44,65,77,79,80,135] Despite the lack of scientific evidence for an association between HPV vaccination and incident CRPS, public disapproval of HPV vaccination following media coverage of CRPS cases led the Japanese government to withdraw its recommendation for HPV vaccination in June 2013.[66] HPV vaccination among eligible adolescents in Japan subsequently fell from 80% to <5% by the end of 2014.[71,136]

The European Medicines Agency (EMA) recently concluded based on evidence from clinical trials, surveillance, and case reports that HPV vaccination does not cause CRPS.[70,137] However, to our knowledge, population-based studies have not been conducted to assess the risk of CRPS in adolescent girls, accounting for physical health status. A case series describing suspected CRPS in 40 Japanese girls reported that onset of CRPS symptoms often occurred long after the first dose of HPV vaccine (mean 5.47±5.00 months).[68] Further, the report did not account for any history of traumatic injury among the cases, neglecting an essential component of CRPS etiology. It is critical to provide rigorous scientific evidence for HPV vaccine safety to prevent further refusal of this potentially life-saving vaccine, and to inform the public about potential risks and contraindications for HPV vaccination.

We present here the results of the first known epidemiological study of the association between HPV vaccination and CRPS incidence in adolescent girls in the United States, comparing the safety of HPV vaccination to that of Tdap and of MenACWY vaccination. We used a large private insurance claims database to identify sufficient adolescent CRPS cases for analysis.

Methods

Data source and study population

The MarketScan® Commercial Claims and Encounters database captures patient-level medical claims for over 200 million unique enrollees in the United States since 1995.[96] MarketScan provides patient demographic data, type and duration of health plan enrollment, claims for medical diagnoses, procedures, and prescriptions using International Classification of Disease – 9th Revision (ICD-9), Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System (HCPCS), and national drug codes (NDC), respectively, and dates of medical services. We obtained MarketScan claims data between January 1, 2000 and December 31, 2014 from Truven Health Analytics.

The study period began June 29, 2006 – the date of the ACIP recommendation for HPV vaccination in girls – and ended December 31, 2014. We included girls who 1) turned 11 years of age between 2006 and 2014; 2) had no prior claims for adolescent vaccination or CRPS; and 3) had at least one year of continuous insurance plan enrollment prior to the 11th birthday. We observed girls from the 11th birthday until the date of a claim for a CRPS diagnosis, or censorship at disenrollment from their insurance plan or December 31, 2014. For girls with multiple continuous enrollment periods, we restricted observation to the enrollment period that included the 11th birthday. Because date of birth is protected health information, we searched

monthly insurance enrollment files to identify the month in which the adolescent's age changed, and then set the date of birth to the last day of that month.

Covariate ascertainment

The primary outcome was a diagnosis of CRPS, based the International Disease Classification of Diseases, Ninth Revision (ICD-9) codes for reflex sympathetic dystrophy (ICD-9 codes 337.2, 337.2X) and algoneurodystrophy or Sudeck's atrophy (ICD-9 code 733.7). We also identified cases of possible CRPS, based on ICD-9 codes for other idiopathic peripheral autonomic neuropathies (ICD-9 codes 337, 337.0, 337.00, 337.09, 337.1, 337.9) and neuralgia (ICD-9 code 729.2). Sensitivity analyses used a composite outcome of CRPS and possible CRPS cases.

The primary exposures were claims for adolescent vaccination, based on Current Procedural Terminology (CPT) codes for administration of 2vHPV (CPT code 90650) or 4vHPV(CPT code 90649); Tdap vaccine (CPT code 90715); or MenACWY vaccine (CPT code 90734). Secondary exposures included 1) concomitant administration of HPV vaccine with one or more of Tdap, MenACWY, or influenza (CPT codes 4037F, 90658-90688, 90724, 90737) vaccines; and 2) concomitant administration of Tdap and MenACWY vaccines with HPV vaccine. Only the first instances of Tdap and MenACWY vaccination were considered for this analysis.

The primary confounder of interest was a historical diagnosis of physical trauma or an occurrence of physical trauma during follow-up. Trauma is positively associated with CRPS incidence, and may also be positively associated with adolescent vaccination through increased opportunities for vaccination during sick visits.[138,139] Historical trauma was measured in the year prior to the 11th birthday, and occurrence of trauma during follow-up was measured from the 11th

birthday until the end of follow-up at CRPS diagnosis or censorship. Physical trauma was ascertained using ICD-9 codes for fractures, dislocations, sprains, and motor vehicle accidents; CPT codes for setting of fractures and dislocations; and CPT codes for surgeries of the musculoskeletal or nervous systems in inpatient and outpatient settings (Appendix 1).

Statistical analysis

We first estimated the incidence rate and 95% confidence interval (CI) for CRPS using generalized estimating equations with a Poisson distribution and a robust variance estimator. Next, we assessed the associations of adolescent vaccinations with incident CRPS using time-dependent Cox models to estimate hazard ratios (HR) and 95% CIs, comparing the hazard of CRPS between vaccinated and unvaccinated girls. We estimated crude HRs and trauma-adjusted HRs.

Vaccination and trauma were considered time-dependent covariates. All girls were unexposed to all vaccinations at the beginning of follow-up. Girls who never received vaccination remained unexposed for the full follow-up period, while girls who received vaccination became exposed at the first date of a claim for vaccination. To assess the association of recent vaccination with CRPS, we considered girls exposed for 30 and 90 days after vaccination. At the end of the exposure window, vaccination status returned to unexposed. In the case of multiple doses of HPV vaccine, vaccination status returned to exposed after a subsequent dose was received, and remained exposed until the end of the exposure window. In a sensitivity analysis, we eliminated the exposure window to assess the hazard of CRPS following any recent or non-recent vaccination; girls with claims for vaccination were considered exposed from the first date of vaccination and for the duration of follow-up. Trauma status was ascertained in a similar fashion. Girls with no claims for trauma remained unexposed for the duration of follow-

up, whereas girls with claims for trauma were considered exposed from the date of the claim and for the duration of follow-up.

Next, we used time-dependent Cox models including interaction terms between vaccinations to assess the hazard of CRPS following receipt of 1) concomitant HPV vaccination versus HPV vaccination alone; and 2) concomitant Tdap+MenACWY+HPV versus Tdap+MenACWY. We estimated crude and trauma-adjusted HRs, and p-values to test the statistical significance of the vaccination interactions.

Finally, we identified additional diagnoses from girls' claims records that were positively associated with CRPS incidence. We identified the 400 most prevalent diagnoses among girls in the sample between the 11th birthday and the end of follow-up at CRPS diagnosis or censorship. We then created binary variables indicating whether or not each girl had the diagnosis. All diagnoses were considered time-dependent covariates using the method described above: girls without the diagnosis remained unexposed for the duration of follow-up, and girls with the diagnosis were considered exposed from the date of the diagnosis claim and for the duration of follow-up. We used time-dependent Cox models to estimate bivariate HRs for the association between each diagnosis and CRPS incidence; similar diagnoses were combined into a composite variable, and new HRs using the composite variable were estimated. Selected diagnoses of interest are displayed in a forest plot, organized by illness category.

All analyses were conducted in SAS version 9.3 (SAS Institute, Cary, North Carolina, USA).

Results

The present analysis included 1,232,572 girls. The median duration of follow-up from the 11th birthday until CRPS diagnosis or censorship was 1.66 years (interquartile range: 0.67-3.25 years). The incidence proportion of HPV vaccination was 23.3%, compared to 50.4% for Tdap and 44.0% for MenACWY vaccination (Table 5.1). 4vHPV was administered in over 98% of all HPV vaccinations. We identified 563 cases of CRPS, with an incidence rate of 20.57 per 100,000 person-years. An additional 1,689 possible CRPS cases were identified for use in sensitivity analyses (Table 5.1).

The relative hazard of CRPS was not elevated within the 30 days following any adolescent vaccination, in crude analysis or after adjustment for trauma (Table 5.2). Within the 90 days following vaccination, HPV vaccination was associated with an increased hazard of CRPS (HR: 1.51, 95% CI: 1.09, 2.09), but this association was null after adjustment for trauma (adjusted HR: 1.30, 95% CI: 1.00, 1.93). After adjustment for trauma, MenACWY vaccination (adjusted HR: 1.54, 95% CI: 1.05, 2.28) and concomitant Tdap+MenACWY vaccination (adjusted HR: 1.67, 95% CI: 1.08, 2.60) were positively associated with CRPS in the 90 days following vaccination (Table 5.2).

In sensitivity analyses eliminating the exposure window, we found no significant association between HPV vaccination at any time in the past and CRPS incidence (Table 5.3). We observed crude associations between Tdap vaccination, MenACWY vaccination, and concomitant Tdap+MenACWY vaccination and incident CRPS (Table 5.3). However, after adjustment for trauma, the HRs for Tdap vaccination (adjusted HR: 1.09, 95% CI: 0.91, 1,29) and MenACWY vaccination (adjusted HR: 1.19, 95% CI: 1.00, 1.42) became non-significant. The adjusted HR for concomitant Tdap+MenACWY vaccination remained significantly elevated after adjustment (adjusted HR: 1.27, 95% CI: 1.06, 1.51) (Table 5.3).

We observed a non-significant increase in CRPS hazard comparing concomitant HPV vaccination to HPV vaccination alone in the past 30 days (adjusted HR: 2.30, 95% CI: 0.80, 6.56) or 90 days (adjusted HR: 1.62, 95% CI: 0.85, 3.06,) (Table 5.4). We also observed a non-significant increase in CRPS hazard comparing concomitant Tdap+Men+HPV vaccination to concomitant Tdap+MenACWY vaccination in the past 30 days (adjusted HR: 4.15, 95% CI: 0.69, 24.48) or 90 days (adjusted HR: 1.35, 95% CI: 0.52, 3.51) (Table 5.4). The p-values for all interaction terms exceeded the 0.05 significance level, indicating no excess CRPS hazard associated with concomitant administration of multiple vaccines.

When including possible CRPS cases in the above analyses, we observed similar trends in which observed associations between HPV, Tdap, MenACWY, or Tdap+MenACWY vaccination at any time in the past were attenuated to the null value after adjusting for trauma. We also saw no association between any vaccination and the 30- or 90-day hazard of CRPS or possible CRPS.

Crude HRs for positive associations between prior diagnoses and incident CRPS are displayed in Figure 5.1. Of the 400 most prevalent prior diagnoses among girls in the sample, 258 were positively associated with incident CRPS; 209 of these were condensed into broader categories, listed on the left side of the figure. The strongest predictors of CRPS were musculoskeletal diagnoses. Girls with injuries, including a fracture, sprain, strain, dislocation, contusion, or wound, had at least twice the hazard of CRPS compared to girls without injuries, and girls with injuries to the lower limb had a 12-fold hazard of CRPS compared to girls without lower limb injuries (HR: 12.4, 95% CI: 10.4, 14.7) (Figure 5.1). Likewise, pain in the lower joints showed a similar magnitude of association with CRPS (HR: 11.8, 95% CI: 8.09, 16.6) (Figure 5.1). Girls with anxiety and adjustment disorders had three times the hazard of CRPS

compared to girls without (HR: 3.12, 95% CI: 2.41, 4.04). Common pediatric illnesses, such as asthma, respiratory and ear infections, asthma, allergies, menstrual irregularities, anemia, and skin disorders, were also positively associated with CRPS (Figure 5.1).

Discussion

This is the first population-based, epidemiological study to assess the association between adolescent vaccination and incident CRPS. The hazard of CRPS was not significantly elevated following HPV vaccination at any time in the past, or in the past 30 or 90 days. We observed an elevated hazard of CRPS following MenACWY vaccination and concomitant Tdap+MenACWY vaccination in the past 90 days, and following concomitant Tdap+MenACWY vaccination at any time in the past. However, we cannot rule out residual confounding of these associations due to unobserved factors; expert opinion suggests that CPRS cases occurring more than 30 days after vaccination are unlikely to be caused by vaccination.[140] We identified additional health status indicators that were positively associated with a CRPS diagnosis. Common pediatric illnesses and healthcare seeking behavior may also confound associations between vaccination and CRPS, and these health indicators should be assessed in future epidemiologic studies of risk factors for CRPS.

We observed CRPS incidence rates comparable to those reported in Minnesota, USA and The Netherlands, both of which included adult CRPS cases.[38,39] To our knowledge, our incidence rate estimate is the only one reported in the literature to be restricted to pediatric cases. Another key difference between our estimates and prior estimates is the choice of data source: our data reflect healthcare usage among insured individuals, whereas previous estimates included population-level healthcare usage data, irrespective of insurance status. As a result, our sample may be biased toward heavier users of healthcare. In accordance with the CRPS literature, we

found that CRPS was highly associated with indicators of ill health. Among CRPS cases in our sample, 79% had an occurrence of trauma prior to CRPS diagnosis. Also consistent with prior reports, a large proportion of CRPS cases in our sample (36%) had a history of mental illness diagnosis or treatment prior to CRPS onset (Appendix 2), supporting a potential psychological component in CRPS development.[45,48,98,132–134] In a Danish case-control study of 316 females seeking care for adverse events following HPV vaccination, matched with 163,910 vaccine recipients not reporting adverse events, cases were more likely to utilize primary care, including phone or email consultations with providers (odds ratio: 2.38, 95% CI: 1.44, 3.92) and requests for laboratory analysis (odds ratio: 1.73, 95% CI: 1.29, 2.32) prior to vaccination.[141] The role of somatization or conversion disorders should be considered in CRPS diagnosis and treatment, and psychotherapy in addition to physical therapy remains a cornerstone of successful pediatric CRPS management.[44–62]

Several biological mechanisms for CRPS have been proposed. First, immune activation and triggering of inflammatory pathways may cause the pain, heat, redness, and swelling that is common in acute CRPS.[42,142,143] In a German hospital-based study, levels of pro-inflammatory molecules interleukin-8 and Substance P were increased in CRPS patients compared to healthy patients.[144] Second, in individuals with underlying dysfunction of the autonomic nervous system, stimulation of dysfunctional nerve fibers, e.g. from injuries, can trigger the disproportional pain sensations that are characteristic of CRPS.[86,145,146] Autonomic dysfunction may be hereditary; a case series from The Netherlands described multiple CRPS cases in families, with an earlier onset and more severe presentation in familial cases compared to sporadic cases.[147] Third, prolonged immobilization of the arm due to pain at the injection site can lead to decreased blood flow and trophic changes to the limb, resembling symptoms of CRPS; injection site pain may be

elevated following concomitant vaccination.[148–150] Future research should continue to search for the pathophysiological mechanisms of CRPS, including mechanisms that might be associated with vaccination (e.g. inflammatory responses following vaccination and nerve injuries caused by needles).

Study limitations include the inability to validate CRPS diagnoses using additional diagnostic data, as this was not available from MarketScan insurance claims. The diagnostic criteria endorsed by the International Association for the Study of Pain (IASP) rely on clinical signs and symptoms that are seldom reported in outpatient medical claims. Further, these criteria were validated in adults, despite a distinct phenotype and prognosis in pediatric cases cases.[42,49] As a result, it is possible that our CRPS incidence estimate, as well as the number of cases identified in Japan, is over-estimated. Two prior studies, in which CRPS cases identified from healthcare databases were validated using medical records and expert review, found that 43-65% of CRPS cases did not fulfill the diagnostic criteria.[38,39] We were also unable to determine if trauma occurred in the same limb(s) affected by CRPS, due to missing data on which limb was affected. Finally, residual confounding by other health indicators may account for the positive associations that we observed between CRPS hazard and MenACWY and Tdap+MenACWY associations in the past 90 days (e.g. infections).

The primary strength of this study is the ability to identify many cases of a rare disease using employer-sponsored insurance claims. MarketScan also provides accurate and unbiased data on vaccinations and dates of service, allowing us to assess multiple vaccination combinations. We used sophisticated time-to-event models to estimate the hazard of CRPS within pre-specified windows following vaccination, providing evidence that CRPS risk is not elevated in the days proximal to a vaccination event and casting doubt on the biological

plausibility of vaccine-induced CRPS. Establishing time frames is critical, as the Japanese case study included cases that happened a median of 5.47 months after vaccination, reducing the probability that these events were incited by the vaccination event.[68] Finally, ours is the first epidemiological study to adjust for the occurrence of trauma when assessing the association of vaccination with CRPS. While there is not strong evidence from the literature that trauma or ill health is associated with increased vaccination rates, we posit that trauma is more likely to influence vaccination rates than the converse. We feel confident that trauma is not along the causal pathway between vaccination and CRPS and thus we did not inappropriately adjust for a mediating variable. Doing so may induce a spurious association between vaccination and CRPS, or may mask a true association that is mediated by trauma.

Our results support the continued administration and co-administration of recommended vaccines to adolescents in the United States. We recommend that this study be replicated using Japanese insurance claims to confirm these findings, and to identify any potential ecological differences between adolescents in the United States and Japan. Future research directions include conducting expert medical record reviews of CRPS cases to validate diagnoses against highly-specific criteria; and assessment of vaccination practices – including the number of injections administered and in which limb – and their association with an increased pain response and subsequent CRPS development. Future studies should also estimate absolute differences in CRPS risk and a "number needed to harm" to estimate the excess CRPS caseload associated with vaccination. Given the rarity of adolescent CRPS, any potential increase in CRPS cases would correspond to a small number, and would not necessarily warrant changing existing vaccination recommendations.

Conclusions

Our findings, in conjunction with those published the EMA, do not support any changes to existing HPV vaccination recommendations with respect to an association with CRPS. While we observed associations between CRPS and MenACWY vaccination and concomitant Tdap+MenACWY vaccination, we suggest further study to identify additional confounders of these relationships. Further study on suspected CRPS risk factors is warranted, as the discovery of independent risk factors could lead to development of CRPS risk assessment tools, and could potentially identify contraindications for adolescent vaccination. Presently, providers should continue to follow ACIP recommendations for injection procedures and for managing syncope, anaphylaxis, and pain following vaccination.[13]

CHAPTER 6: CONCLUSIONS

Summary of findings

This work found that among 1.7 million age-eligible adolescents in the United States, HPV vaccination uptake is lower than Tdap and MenACWY vaccination uptake, in agreement with nationwide vaccination coverage rates. The age at first uptake of HPV vaccination is older than that for Tdap and MenACWY vaccination, indicating that many adolescents are receiving HPV vaccination after the ACIP-recommended age, and are at increased risk for HPV infection and harmful sequelae. By the end of follow-up in our sample, only one-quarter of vaccinated adolescents had received all three ACIP-recommended vaccines.

Geographic factors were associated with adolescent vaccination, wherein rural adolescents were less likely than urban adolescents to receive HPV, Tdap, and MenACWY vaccination. However, the effect of urbanicity on vaccination rates was modified by region: whereas rural adolescents in the North Central, South, and West regions were less likely to receive adolescent vaccination, rural adolescents in the Northeast region were *more* likely to receive HPV vaccination.

We observed some positive trends in HPV vaccination by birth cohort. Concomitant administration of HPV vaccine alongside Tdap and MenACWY increased steadily with each successive birth cohort, as did the cumulative incidence of timely HPV vaccination at age 11 or 12.

In over 1.2 million adolescent girls, we observed 563 cases of CRPS, for an incidence rate of 20.6/100,000 person-years. We found no significant increase in the hazard of CRPS

comparing girls with and without recent adolescent vaccination, or concomitant adolescent vaccination, within the past 30 or 90 days. Sensitivity analyses also showed that incidence of CRPS at any time following adolescent vaccination was heavily confounded by experiencing or having a history of physical trauma. While bivariate analyses indicated a positive association between Tdap and MenACWY vaccination and CRPS at any time since vaccination, adjustment for trauma attenuated all associations toward the null value. We also found that concomitant administration of Tdap, MenACWY, or influenza vaccine with HPV vaccine was not associated with an increased hazard CRPS or possible CRPS within 30 or 90 days, nor was concomitant administration of HPV with Tdap+MenACWY.

We did observe positive associations between MenACWY vaccination and Tdap+MenACWY vaccination and the hazard of CRPS after 90 days, as well as Tdap+MenACWY vaccination and the hazard of CRPS at any time following vaccination. However, these associations were attenuated after adjustment for trauma, and thus we cannot rule out residual confounding due to other health-related factors. In a series of bivariate analyses, we identified lower limb injuries as the primary risk factor for CRPS, in agreement with prior studies and current understandings on CRPS etiology in adolescents. Common pediatric illnesses were also found to be associated with CRPS incidence, and may also confound observed associations between vaccination and CRPS. Infections, asthma and allergies, and mental illness may be targets for future research to better understand the etiology of CRPS.

Public health significance

The low rates of HPV vaccination relative to Tdap and MenACWY vaccination indicate vast missed opportunities for HPV vaccination. The findings from our study can be used to identify targeted and tailored strategies to increase the use of all recommended adolescent

vaccines, and specifically HPV vaccine. In general, improved communication between providers and caregivers can provide needed information on the effectiveness and safety of HPV vaccines to help caregivers make informed vaccination decisions.

From a vaccine policy standpoint, states can develop programs to improve availability of vaccines or access to vaccination. While our study population includes insured adolescents who have greater financial access to vaccination, there may be geographical or logistical barriers that prevent widespread vaccination in certain areas. For example, rural areas in large geographic regions, such as the North Central, South, and West regions, may be more isolated from health care centers or providers who offer HPV vaccination. HPV vaccination in boys is also lower than in girls, despite a gender-neutral HPV vaccination recommendation in the United States. HPV vaccination in boys not only reduces the risk for anal, penile, and oropharyngeal cancer, but also prevents transmission to girls and contributes to reducing the burden of high-risk HP V and cervical precancer. To see a continuation of the positive cohort effects we observed with respect to timely HPV vaccination and concomitant administration of HPV with other vaccines, a combination of approaches will be needed to improve access to and demand for HPV vaccination among adolescents.

A growing evidence base for HPV vaccine safety with respect to SAEs can improve perceptions of the vaccine among providers and caregivers and allay fears that HPV vaccines are riskier than other commonly-administered adolescent vaccines. Our study supports prior evidence from clinical trials and post-licensure surveillance to show that HPV vaccination does not confer an elevated risk of CRPS or CRPS-like conditions. Known risk factors for CRPS are also associated with receipt of HPV vaccination through increased utilization of the health care system, and thus crude associations between vaccination and CRPS appeared positive in our

analyses. The case study that contributed to the withdrawal of HPV vaccination in Japan neglected to document the health history of CRPS patients, and was remiss in attributing the patients' symptoms exclusively to HPV vaccination. Our findings demonstrate that physical trauma accounts for much of the observed association between vaccination and CRPS, making the case for conditioning on these variable in future epidemiological studies of CRPS. Further, case studies that report on SAEs following vaccination should take care to thoroughly document patients' medical history to expound upon prior or existing conditions that may account for the observed signs and symptoms. Rigorous research and responsible reporting thereof can prevent a recurrence of the situation in Japan, in which decisions that affect millions of vulnerable individuals were made in response to public perceptions and in the absence of sufficient scientific evidence.

Strengths

The primary strength of this study include a large sample to 1) identify trends in adolescent vaccination and 2) identify rare SAEs for analysis. We had sufficient numbers of adolescents to be able to stratify by key characteristics and identify coverage gaps by region and urbanicity, as well as observe cohort effects for HPV vaccination practices. We were also able to conduct the first population-based epidemiological study of HPV vaccination and CRPS, providing evidence to reinstate the HPV vaccination recommendation in Japan and continuing to provide assurance that SAEs following vaccination are rare and are likely not associated with the vaccination itself. Using healthcare data allowed us to assess confounding due to other health-related factors that we could capture in insurance claims records. For both aims, insurance claims afforded us data that does not require sampling and is more accessible than survey data, and is not subject to the same recall biases as survey data.

We used rigorous longitudinal methods to estimate associations between vaccination and CRPS, accounting for time since vaccination and administration of multiple vaccines concomitantly. Having dates of service for vaccination, CRPS diagnosis, and other health encounters of interest provided clarity on the temporality of all covariates for a proper epidemiological study of post-vaccination SAEs.

Limitations

Limitations of this work include limited follow-up time for observing vaccination events of interest. As a result, we were unable to assess HPV dose completion for all adolescents. Given the open nature of our cohort, we were also unable to assess vaccine coverage per se, and instead estimated vaccination proportions that are not directly comparable to the coverage rates reported in the NIS-Teen survey. Insurance claims also lack race/ethnicity information and prevent us from identifying potential cultural differences in vaccination practices across the United States. Given that our study population is insured by an employer-sponsored plan, our studies' findings are not likely generalizable to low-income or Medicaid-eligible populations.

CRPS is a poorly-understood outcome that is diagnosed on strictly clinical criteria. Without a straight-forward diagnostic tool, and given the low specificity of early versions of the IASP diagnostic criteria, misdiagnosis of CRPS cases is common. Prior studies of CRPS incidence in Minnesota, USA and The Netherlands also used healthcare databases to identify CRPS cases, but validated these diagnoses using electronic medical records and expert opinion, subsequently reduced the initial case counts in both studies.[38,39] Without access to medical records, and without systematic documentation of signs and symptoms in insurance claims, we were unable to validate our CRPS cases. Insurance claims also lack the richness of data of medical records, preventing us from clarifying the physiological mechanisms of CRPS

development, e.g. if the limb that experienced trauma is the same that experienced CRPS symptoms.

Future research directions

Future research on adolescent HPV vaccination in the United States should aim to understand regional differences in vaccination patterns, with specific focus on availability and access to vaccines. Prior studies have identified caregivers' barriers to HPV vaccination, as well as effective messages from providers to promote acceptance of HPV vaccination. Federal and local public health entities should develop training and educational materials for providers to engage in evidence-based communications with caregivers about the importance of adolescent vaccination. Additional data will be needed to identify further characteristics adolescents who do not receive HPV vaccination and to create targeted interventions to improve uptake. Other factors of interest include race/ethnicity, primary language spoken at home, education status of caregivers, and religion. We should continue to monitor vaccination trends throughout the United States, including patterns of use of the new 9-valent HPV vaccine once sufficient utilization data become available.

The safety of HPV and other adolescent vaccines must be continuously examined. Now that HPV vaccines have been approved in the United States for over 10 years, uptake rates are increasing to approach the rates of Tdap and MenACWY vaccines. However, anxiety around HPV vaccine safety persists, and the scientific community must take seriously any reports of SAEs following vaccination. Rigorous safety studies can reassure policy-makers, providers, and caregivers that HPV vaccination is not associated with SAEs, or can identify specific risk factors for SAEs that may be incorporated in vaccination recommendations. Though not without limitations, insurance claims data have proven to be useful data sources for identifying rare

events, and can be used to assess vaccine safety with respect to myriad outcomes. Safety studies for rare events of unknown etiology, like CRPS and many auto-immune diseases, can be supplemented by thorough medical record reviews that provide detailed data on health history, signs, symptoms, and diagnostics. Triangulation of safety data from multiple sources can provide the most comprehensive evidence in favor of life-saving adolescent vaccination, or can provide critical insights into risk factors for SAEs and contraindications for vaccination.

Table 4.1. Incidence of HPV, Tdap, and MenACWY vaccination among adolescents in the MarketScan database, 2009-2014

Incidence of vaccination	**Overall (n=1,691,223)**	**Girls (n= 822,554)**	**Boys (n=868,669)**
Median duration (IQR) of follow-up, months	16.1 (7.1, 31.2)	16.1 (7.1, 31.2)	16.1 (7.1, 31.2)
Cumulative incidence (incidence proportion) of adolescent vaccination			
Any vaccination	948,995 (56.1%)	467,355 (56.8%)	481,640 (55.5%)
HPV vaccination	311,110 (18.4%)	180,373 (21.9%)	130,737 (15.1%)
Tdap vaccination	880,586 (52.1%)	431,814 (52.5%)	448,772 (51.7%)
MenACWY vaccination	774,132 (45.8%)	378,377 (46.0%)	395,755 (45.6%)
	Overall (n=948,995)	**Girls (n=467,355)**	**Boys (n=481,640)**
Mean age (SD) at first adolescent vaccination	11.5 (0.8)	11.5 (0.8)	11.5 (0.8)
HPV vaccination (n=311,110)	11.8 (1.0)	11.7 (1.0)	12.0 (1.1)
Tdap vaccination (n=880,586)	11.2 (0.5)	11.2 (0.5)	11.3 (0.5)
MenACWY vaccination (n=774,132)	11.2 (0.6)	11.3 (0.6)	11.3 (0.6)

Eligible 11-year-olds are those who are continuously enrolled in an insurance plan as of the midpoint of their 11th year and had not previously received HPV/Tdap/MenACWY vaccines. The Advisory Committee on Immunization Practices recommends all three vaccines beginning at age 11.
Abbreviations: HPV=human papillomavirus vaccine; Tdap=tetanus-diphtheria-acellular pertussis vaccine; MenACWY=meningococcal conjugate vaccine; IQR=interquartile range; SD=standard deviation.

Table 4.2. Service-related characteristics at the time of vaccination among adolescents who received HPV, Tdap, or MenACWY vaccination, 2009-2014 (N=948,995)

	Girls (n=467,355)						Boys (n=481,640)					
Characteristic	**HPV (n=180,373)**		**Tdap (n=431,814)**		**MenACWY (n=378,377)**		**HPV (n=130,737)**		**Tdap (n=448,772)**		**MenACWY (n=395,755)**	
Age at initiation (years)	n	%	n	%	n	%	n	%	n	%	n	%
11	96,102	53.3%	342,704	79.4%	292,327	77.3%	57,760	44.2%	351,439	78.3%	302,512	76.4%
12	50,465	28.0%	80,015	18.5%	72,448	19.1%	36,497	27.9%	86,199	19.2%	78,131	19.7%
13	21,240	11.8%	7,398	1.7%	9,759	2.6%	21,547	16.5%	9,271	2.1%	11,187	2.8%
14	10,101	5.6%	1,423	0.3%	3,131	0.8%	11,798	9.0%	1,645	0.4%	3,225	0.8%
15	2,408	1.3%	269	0.1%	653	0.2%	3,065	2.3%	209	0.0%	625	0.2%
16	57	0.0%	5	0.0%	59	0.0%	70	0.1%	9	0.0%	75	0.0%
Provider type at vaccination												
Pediatrician	117,924	65.4%	279,333	64.7%	261,582	69.1%	90,361	69.1%	291,851	65.0%	275,378	69.6%
Family practice	26,179	14.5%	63,321	14.7%	43,310	11.4%	15,745	12.0%	66,556	14.8%	45,543	11.5%
Multi-specialty physician group	7,512	4.2%	17,303	4.0%	14,175	3.7%	5,325	4.1%	17,899	4.0%	14,717	3.7%
Medical doctor	7,198	4.0%	18,670	4.3%	15,969	4.2%	5,078	3.9%	19,338	4.3%	16,686	4.2%
Perinatal medicine	2,532	1.4%	6,319	1.5%	5,736	1.5%	1,662	1.3%	6,532	1.5%	5,916	1.5%
Internal medicine	3,375	1.9%	8,236	1.9%	6,516	1.7%	2,328	1.8%	8,752	2.0%	6,919	1.7%
Nurse	3,265	1.8%	8,032	1.9%	6,398	1.7%	1,790	1.4%	6,756	1.5%	5,219	1.3%
Other*	6,989	3.9%	16,618	3.8%	13,230	3.5%	5,264	4.0%	16,892	3.8%	13,620	3.4%
Missing	5,399	3.0%	13,982	3.2%	11,461	3.0%	3,184	2.4%	14,196	3.2%	11,757	3.0%
HPV vaccine type received												
Quadrivalent	177,831	98.6%	-	-	-	-	130,603	99.9%	-	-	-	-
Bivalent	2,542	1.4%	-	-	-	-	134	0.1%	-	-	-	-

Abbreviations: HPV=human papillomavirus vaccine; Tdap=tetanus-diphtheria-acellular pertussis vaccine; MenACWY=meningococcal conjugate vaccine.
*Other providers include: acute care hospital, allergy & immunology, anesthesiology, birthing center, cardiothoracic surgery, chiropractor, dental specialist, dentist, dermatology, emergency medicine, endocrinology & metabolism, geriatric medicine, hospice facility, hospitalist, infectious diseases, laboratory, medical technician, neurology, obstetrician/gynecologist, ophthalmology, osteopathic medicine, pathology, pediatric allergy & immunology, pediatric cardiology, pediatric emergency medicine, pediatric hematology-oncology, pediatric infectious diseases, pediatric pulmonology, pediatric surgery, physical medicine and rehabilitation, physician assistant, podiatrist, preventive medicine, psychiatry, public health agency, radiology, supply center, unspecified provider, urgent care facility.

Table 4.3. Incidence rates per 10,000 person-months of HPV, Tdap, and MenACWY vaccination among adolescents by selected characteristics, 2009-2014 (n=1,691,223)

	HPV	Tdap	MenACWY
	IR (95% CI)	**IR (95% CI)**	**IR (95% CI)**
Metropolitan statistical area			
Urban (n=1,423,989)	103.9 (103.5, 104.2)	527.5 (526.0, 528.9)	414.9 (413.7, 416.1)
Rural (n=231,792)	78.8 (77.9, 79.6)	304.5 (302.3, 306.8)	221.8 (220.0, 223.6)
Missing (n=35,442)			
Region of residence			
Northeast (n=247,991)	104.3 (103.4, 105.2)	685.3 (680.3, 690.3)	526.8 (532.1, 530.6)
North Central (n=426,605)	99.3 (98.7, 100.0)	542.8 (540.1, 545.4)	417.2 (415.0, 419.3)
South (n=637,009)	91.3 (90.8, 91.8)	446.9 (445.1, 448.7)	364.1 (362.5, 365.7)
West (n=343,161)	117.2 (116.3, 118.0)	404.7 (402.4, 407.1)	299.7 (297.8, 301.5)
Missing (n=36,457)			
Insurance plan type			
Preferred provider plan (n=1,043,991)	96.8 (96.4, 97.3)	484.5 (482.9, 486.1)	373.4 (372.2, 374.7)
Comprehensive (n=18,649)	81.5 (78.9, 84.3)	423.4 (412.5, 434.6)	330.5 (321.8, 339.4)
Managed care plan (n=332,193)	109.5 (108.8, 110.3)	458.8 (456.1, 461.5)	364.6 (362.4, 366.8)
High deductible plan (n=244,662)	105.5 (104.6, 106.3)	575.2 (571.5, 579.0)	454.0 (451.0, 457.0)
Missing (n= 51,728)			
Received primary care in the past year			
No (n=1,493,373)	98.4 (98.1, 98.8)	472.6 (471.4, 473.9)	368.0 (366.9, 369.0)
Yes (n=197,850)	119.8 (118.7, 120.9)	676.3 (671.4, 681.2)	533.9 (530.0, 537.9)

Abbreviations: IR=incidence rate; CI=confidence interval; HPV=human papillomavirus vaccine; Tdap=tetanus-diphtheria-acellular pertussis vaccine; MenACWY=meningococcal conjugate vaccine.

Table 4.4. Incidence rate ratios for the association of urbanicity with HPV, Tdap, and MenACWY vaccination among adolescents, stratified by region, 2009-2014

		HPV IRR (95% CI)	Tdap IRR (95% CI)	Men IRR (95% CI)
All Regions (n=1,655,781)*	Urban	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Rural	**0.76 (0.75, 0.77)**	**0.58 (0.57, 0.58)**	**0.53 (0.53, 0.54)**
Northeast (n=247,991)	Urban	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Rural	**1.09 (1.05, 1.13)**	**0.86 (0.84, 0.88)**	**0.79 (0.77, 0.82)**
North Central (n=426,605)	Urban	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Rural	**0.76 (0.74, 0.77)**	**0.50 (0.49, 0.50)**	**0.46 (0.46, 0.47)**
South (n=637,009)	Urban	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Rural	**0.77 (0.75, 0.78)**	**0.60 (0.59, 0.60)**	**0.55 (0.54, 0.56)**
West (n=343,161)	Urban	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Rural	**0.68 (0.66, 0.71)**	**0.55 (0.54, 0.57)**	**0.46 (0.45, 0.47)**

Abbreviations: IRR=incidence rate ratio; CI=confidence interval; MSA=metropolitan statistical area; HPV=human papillomavirus vaccine; Tdap=tetanus-diphtheria-acellular pertussis vaccine; MenACWY=meningococcal conjugate vaccine.

*35,442 observations missing region status.

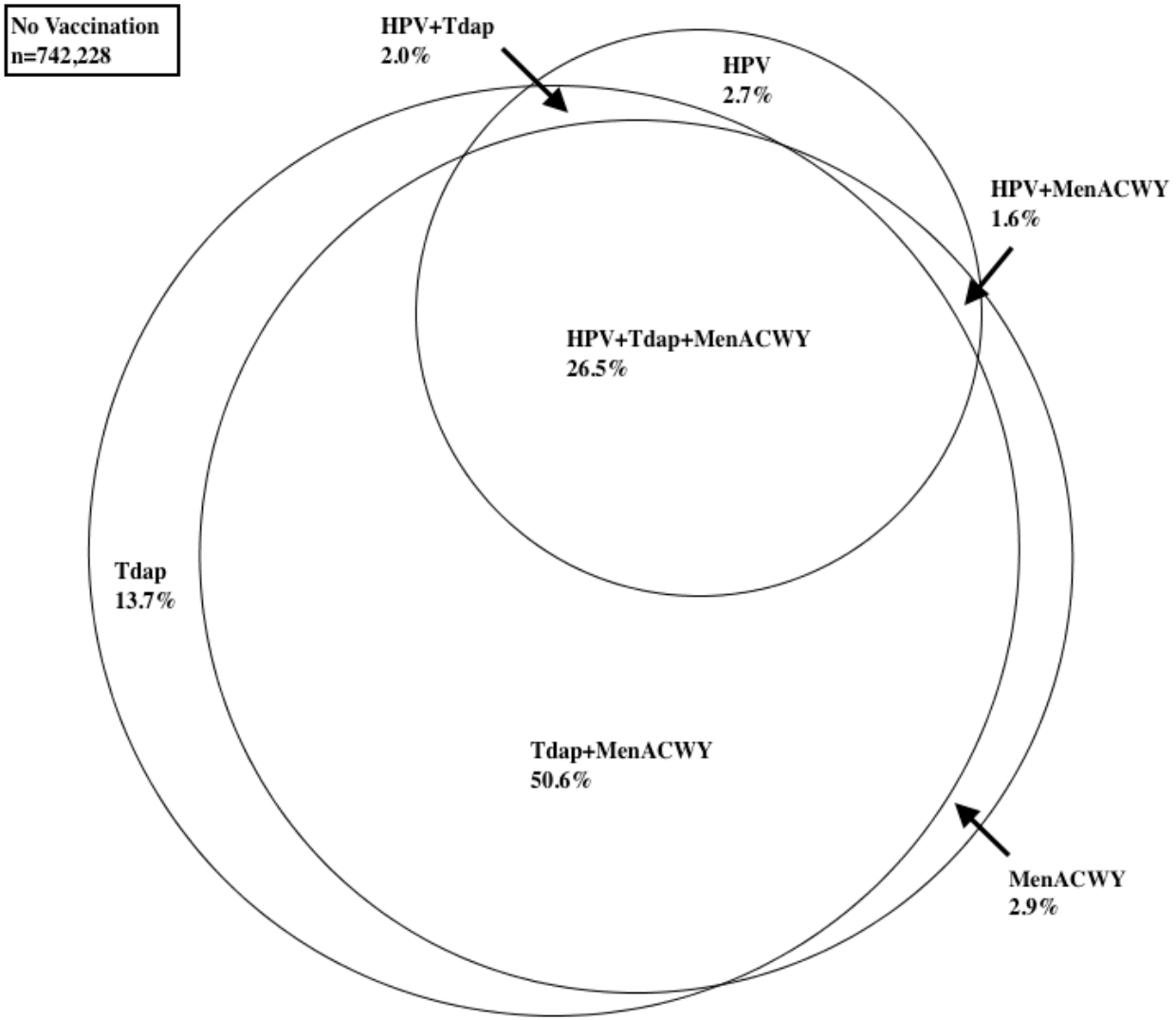


Figure 4.1. Combinations of vaccinations received among adolescents who received any vaccination during follow-up. The combinations represent all vaccinations received during follow-up, regardless of receipt in the same or separate clinic visits.

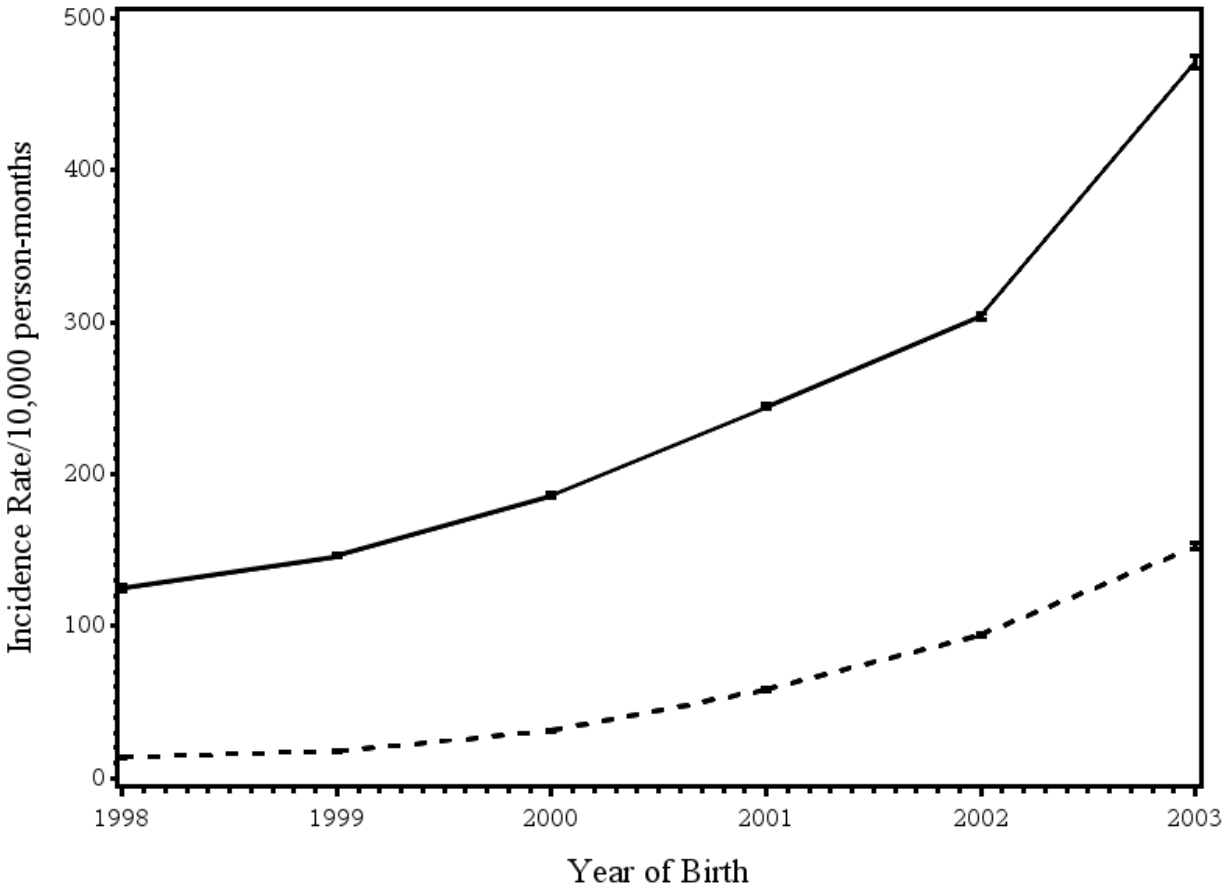


Figure 4.2. Incidence rates per 10,000 person-months of receiving Tdap+MenACWY vaccination in the same visit, and HPV+Tdap+MenACWY vaccination in the same visit. Incidence rates are stratified by birth year to demonstrate cohort effects on co-administration. The solid line represents Tdap+MenACWY, and the dashed line represents HPV+Tdap+MenACWY.

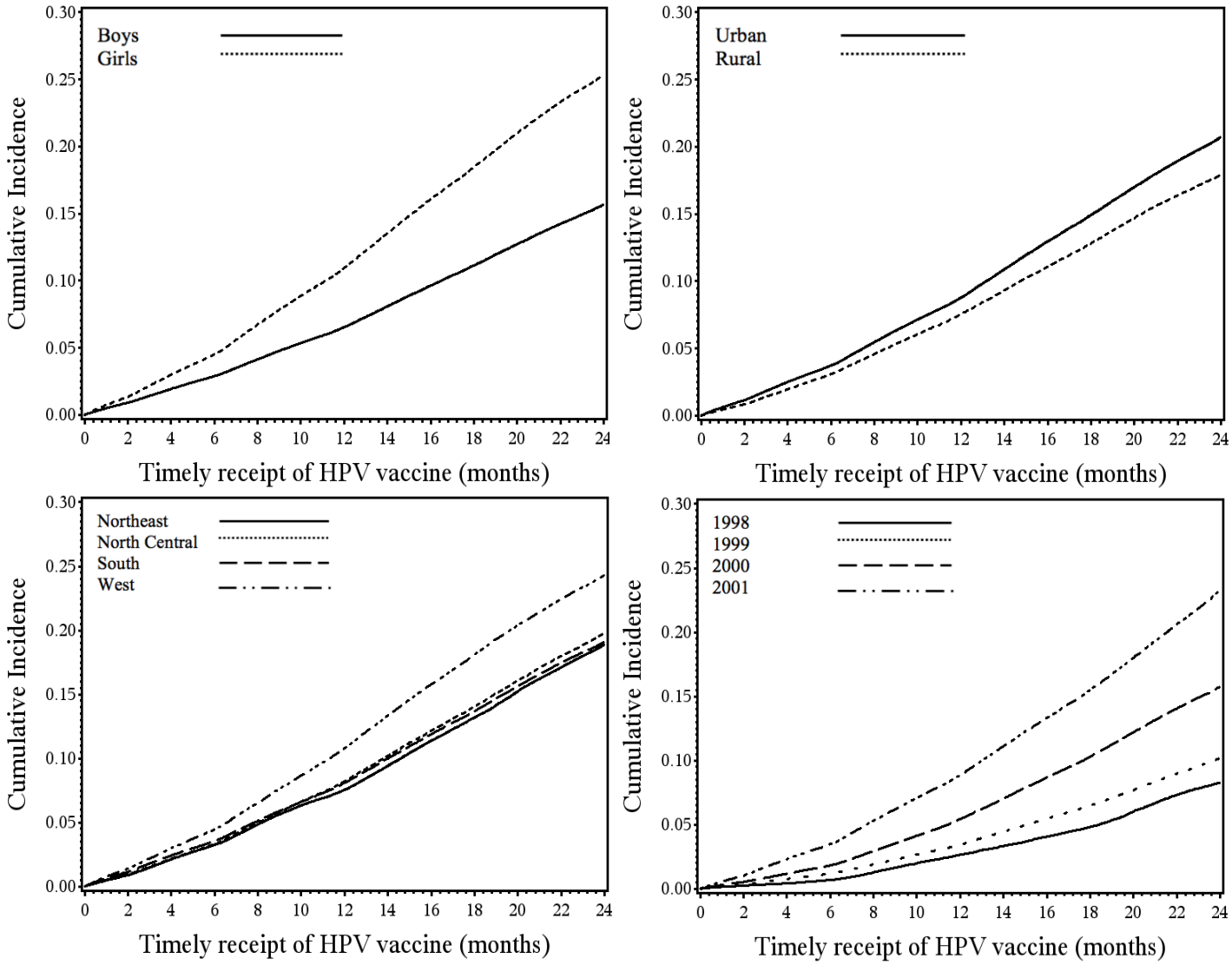


Figure 4.3. Cumulative incidence curves for HPV vaccination within the ACIP-recommended age range, showing differences in timely HPV vaccination, stratified by sex, urbanicity, region, and birth cohort.

Table 5.1. Incidence of adolescent vaccination and complex regional pain syndrome among adolescent girls, 2006-2014 (N=1,232,572)

Median duration of follow-up (IQR), years	1.66 (0.67, 3.25)
Cumulative incidence (incidence proportion) of adolescent vaccination	
HPV vaccination	286,965 (23.3%)
Tdap vaccination	621,342 (50.4%)
MenACWY vaccination	542,105 (44.0%)
Tdap+MenACWY vaccination	437,414 (35.5%)
HPV+Tdap+MenACWY vaccination	219,238 (17.8%)
Cumulative incidence (incidence proportion) of CRPS*	563 (0.045%)
Cumulative incidence (incidence proportion) of possible CRPS †	1,689 (0.14%)
Incidence rate (95% CI) of CRPS per 100,000 person-years	20.57 (18.94, 22.34)

Abbreviations: IQR=interquartile range; HPV=human papillomavirus vaccine; Tdap=tetanus-diphtheria-acellular pertussis vaccine; MenACWY=meningococcal conjugate vaccine; 4vHPV=quadrivalent HPV vaccine; 2vHPV=bivalent HPV vaccine; CRPS=complex regional pain syndrome; CI=confidence interval.

*CRPS cases include diagnoses of reflex sympathetic dystrophy and algoneurodystrophy.

†Possible CRPS cases include diagnoses for neuralgia and other idiopathic peripheral autonomic neuropathies.

Table 5.2. Relative hazard of CRPS among adolescent girls within 30 and 90 days following adolescent vaccination, 2006-2014 (N=1,232,572)

	Within 30 days of vaccination		Within 90 days of vaccination	
	Crude HR (95% CI)	Adjusted HR* (95% CI)	Crude HR (95% CI)	Adjusted HR* (95% CI)
HPV vaccination				
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	1.48 (0.87, 2.51)	1.41 (0.83, 2.40)	**1.51 (1.09, 2.09)**	1.39 (1.00, 1.93)
Tdap vaccination				
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	0.86 (0.43, 1.73)	1.29 (0.64, 2.59)	1.00 (0.67, 1.47)	1.43 (0.97, 2.11)
MenACWY vaccination				
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	0.86 (0.41, 1.81)	1.21 (0.57, 2.55)	1.14 (0.77, 1.68)	**1.54 (1.05, 2.28)**
Tdap+MenACWY vaccination				
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	0.76 (0.31, 1.83)	1.21 (0.50, 2,93)	1.10 (0.71, 1.70)	**1.67 (1.08, 2.60)**

Abbreviations: HPV=human papillomavirus vaccine; Tdap=tetanus-diphtheria-acellular pertussis vaccine; MenACWY=meningococcal conjugate vaccine; CRPS=complex regional pain syndrome; HR=hazard ratio; CI=confidence interval.

*Adjusted for a history of physical trauma and occurrence of physical trauma during follow-up.

Table 5.3. Relative hazard of CRPS among adolescent girls at any time following adolescent vaccination, 2006-2014 (N=1,232,572)

	Crude HR (95% CI)	Adjusted HR* (95% CI)
Ever received HPV vaccination		
No	1.0 (ref)	1.0 (ref)
Yes	1.19 (0.98, 1.46)	**0.81 (0.66, 0.99)**
Ever received Tdap vaccination		
No	1.0 (ref)	1.0 (ref)
Yes	**1.59 (1.34, 1.89)**	1.09 (0.91, 1.29)
Ever received MenACWY vaccination		
No	1.0 (ref)	1.0 (ref)
Yes	**1.70 (1.43, 2.02)**	1.19 (1.00, 1.42)
Ever received concomitant Tdap+MenACWY vaccination		
No	1.0 (ref)	1.0 (ref)
Yes	**1.56 (1.31, 1.85)**	**1.27 (1.06, 1.51)**

Abbreviations: HPV=human papillomavirus vaccine; Tdap=tetanus-diphtheria-acellular pertussis vaccine; MenACWY=meningococcal conjugate vaccine; CRPS=complex regional pain syndrome; HR=hazard ratio; CI=confidence interval.
*Adjusted for a history of physical trauma and occurrence of physical trauma during follow-up.

Table 5.4. Relative hazard of CRPS among adolescent girls following concomitant adolescent vaccination in the past 30 or 90 days, 2006-2014 (N=1,232,572)

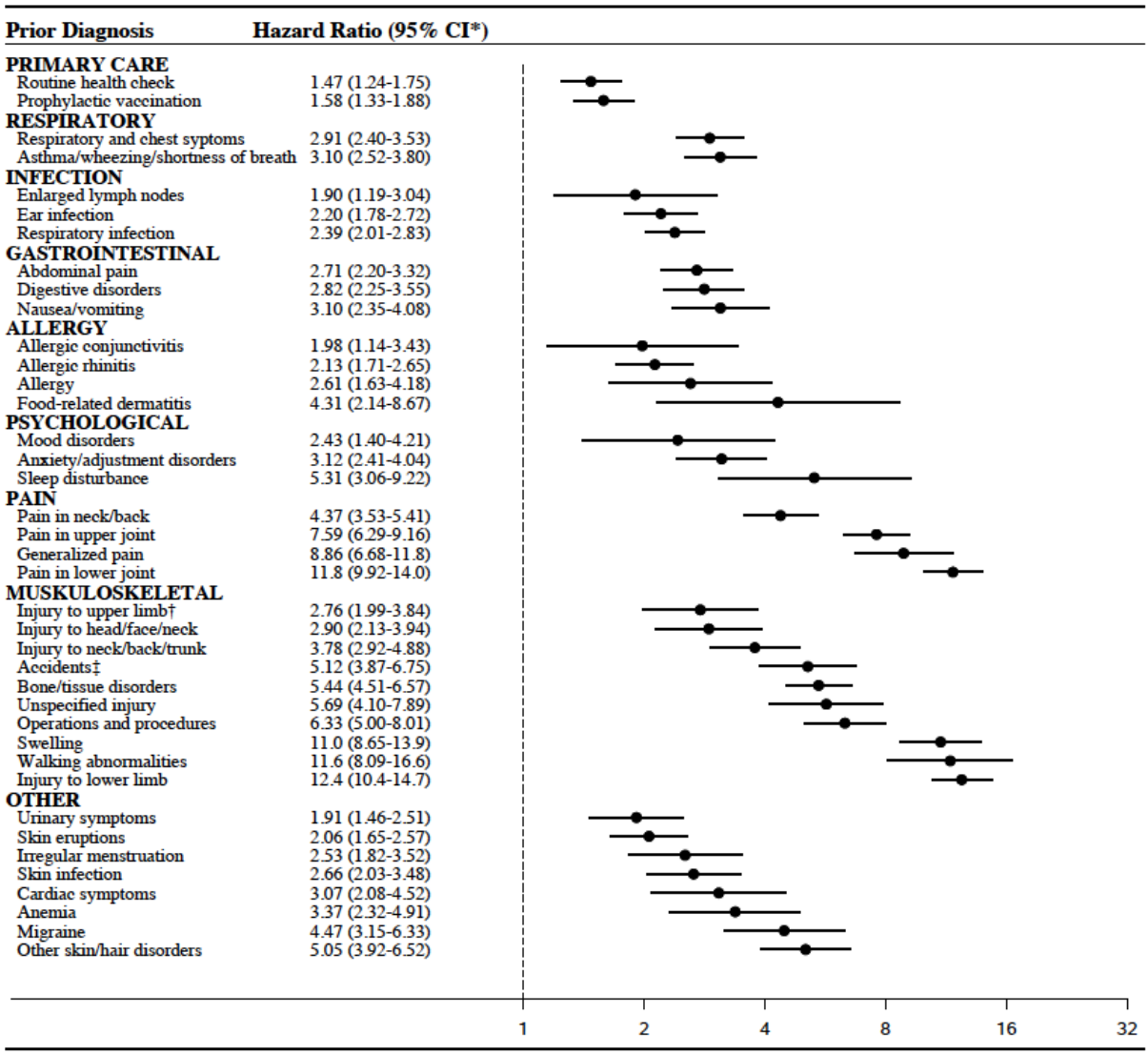
	Vaccinated in past 30 days		Vaccinated in past 90 days	
	Adjusted HR (95% CI) ‡	P for interaction	Adjusted HR (95% CI) ‡	P for interaction
HPV only	1.0 (ref)		1.0 (ref)	
HPV + Tdap/MenACWY/Influenza*	2.30 (0.80, 6.56)	0.25	1.62 (0.85, 3.06)	0.76
Tdap+MenACWY only	1.0 (ref)		1.0 (ref)	
Tdap+MenACWY+HPV †	4.15 (0.69, 24.84)	0.25	1.35 (0.52, 3.51)	0.75

Abbreviations: HPV=human papillomavirus vaccine; Tdap=tetanus-diphtheria-acellular pertussis vaccine; MenACWY=meningococcal conjugate vaccine; CRPS=complex regional pain syndrome; HR=hazard ratio; CI=confidence interval.

*Model includes an interaction term representing receipt of HPV vaccination and receipt of Tdap, MenACWY, or influenza vaccination.

†Model includes an interaction term representing receipt of concomitant Tdap+MenACWY vaccination and receipt of HPV vaccination.

‡ HR for main vaccination, adjusted for interaction with other vaccinations and occurrence of physical trauma during follow-up.



*Hazard ratios compare girls who had the diagnoses during follow-up to those who did not.
†Injuries include fractures, sprains, strains, contusions, dislocations, wounds, and other unspecified injuries.
‡Accidents include falls, striking against people or objects, and sudden strenuous movements.

Figure 5.1. Relative hazard of CRPS following common diagnoses in adolescent girls, 2006-2014 (n=1,232,572)

APPENDIX 1: DIAGNOSES AND PROCEDURES FOR PHYSICAL TRAUMA

Appendix 1. Diagnoses and procedures for physical trauma

Diagnosis	**Description**	**ICD-9 Codes**
Fracture	Pelvis	808, 808.x, 808.xx
	Trunk	809, 809.x
	Upper body: Trunk, shoulder, arm, wrist, hand, finger	810.x-819.x
	Lower body: Thigh, leg, knee, ankle, toe	820.x-828x
	Unspecified bones	829, 829.x
Dislocation	Upper body: Shoulder, elbow, wrist, finger	831.x-834.x
	Lower body: Hip, knee, ankle, foot	835.x-838.x
	Other, multiple dislocations	839, 839.x, 839.xx
Sprain, strain	Upper body: Shoulder, arm, elbow, wrist, hand	840.x-842.x
	Lower body: hip, thigh, leg, knee, ankle, foot	843.x-846.x
	Other, unspecified parts of back	847, 847.x
	Other ill-defined	848, 848.x
Road vehicle accidents	Traffic accident	E81, E81.x, E81.xx
	Non-traffic accident	E82, E82.x, E82.xx
Procedure	**Description**	**CPT/HCPCS Codes**
Surgeries, treatment of fractures and dislocations	Upper body: Shoulder, elbow, arm, wrist, hand, finger	23000-26989
	Lower body: Pelvis, thigh, leg, knee, ankle, foot, toe	26990-28899
	Extracranial nerves, peripheral nerves, autonomic nervous system	64400-64999
Casting, splinting, strapping	Upper body: Body, shoulder, arm, wrist, hand, finger	29000-29280
	Lower body: Hip, leg, knee, foot	29305-29590
	Cast: Removal, revision	29700-29799
Medical equipment	Immobilization devices	L21x-L39x, L43x, L46x
	Canes, crutches, walker, wheelchair, gait trainer	E0100-E0149, E0950-E1298, E2201-E2633, K0001-K0902
	Cast, splint supplies	Q4001-Q4051

APPENDIX 2: DIAGNOSES, PROCEDURES, AND PRESCRIPTION DRUGS FOR MENTAL ILLNESS

Appendix 2. Diagnoses, procedures, and prescription drugs for mental illness	
Diagnosis	**ICD-9 Codes**
Transient mental disorders	293, 293.x, 293.xx
Schizophrenic disorders	295, 295.x, 295.xx
Episodic mood disorders	296, 296.x, 296.xx
Delusional disorders	297, 297.x
Non-organic psychoses	298, 298.x
Anxiety, dissociative, and somatoform disorders	300, 300.x, 300.xx,
Personality disorders	301, 301.x, 301.xx
Physiological malfunction arising from mental factors	306, 306.x, 306.xx
Special syndromes or symptoms, not elsewhere classified (including sleep disorders, eating disorders, pain disorders)	307, 307.x, 307.xx
Acute reactions to stress	308, 308.x,
Adjustment disorders	309, 309.x, 309.xx
Non-psychotic mental disorders	310, 310.x, 310.xx
Depressive disorder, not elsewhere classified	311
Conduct disorders	312, 312.x, 312.xx
Emotional disturbance	313, 313.x, 313.xx
Hyperkinetic disorders	314, 314.x, 314.xx
Procedure	**CPT Codes**
Psychotherapy, psychiatric diagnostic examination	908xx, G007x, G008x, G0090-G0094, 4060f, 4062f, G0410, G0411
Prescription	**Generic Drug Name**
Anti-anxiety drugs	Alprazolam, buspirone, hydroxizine, lorazepam
Antidepressant drugs	Amitriptyline, bupropion, citalopram, clomipramine, desipramine, doxepin, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nortriptyline, paroxetine, phenelzine, sertraline, tranylcypromine, trazodone, venlafaxine
Antipsychotic drugs	Aripiprazole, chlorpromazine, clozapine, fluphenazine, haloperidol, lithium, olanzapine, paliperiodone, perphenazine, prochlorperazine, quetiapine, risperidone, thiothixine, trifluoperazine, ziprasidone
Sleep aids	Chloral hydrate, estazolam, eszopiclone, ramelteon, temazepam, zaleplon, zolpidem
Hyperactivity, narcolepsy drugs	Amphetamine salt combination, atomoxetine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methylphenidate, modafinil

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