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Significant Declines in Juvenile-onset Recurrent Respiratory Papillomatosis Following Human Papillomavirus (HPV) Vaccine Introduction in the United States

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Abstract

Background.—Juvenile-onset recurrent respiratory papillomatosis (JORRP) is a rare and serious disease caused by human papillomavirus (HPV) presumably acquired during vaginal delivery. HPV vaccination of females through age 26 years, recommended in the United States since 2006, can prevent HPV transmission. We assessed trends in JORRP cases before and after HPV vaccine introduction in the United States.

Methods.—Case-patients were identified from 26 pediatric otolaryngology centers in 23 U.S. states. Demographics and clinical history were abstracted from medical records. Case-patients were grouped by year of birth, and birth-cohort incidences were calculated using number of births from either national or state-level natality data from the 23 states. We calculated incidence rate ratios (IRR) and 95% confidence intervals (CI) in 2-year intervals.

Results.—We identified 576 U.S. JORRP case-patients born in 2004–2013. Median age at diagnosis was 3.4 years (interquartile range: 1.9, 5.5). Number of identified JORRP case-patients declined from a baseline of 165 born in 2004–2005 to 36 born in 2012–2013. Incidence of JORRP per 100 000 births using national data declined from 2.0 cases in 2004–2005 to 0.5 cases in 2012–2013 (IRR = 0.2, 95% CI = .1–.4); incidence using state-level data declined from 2.9 cases in 2004–2005 to 0.7 cases in 2012–2013 (IRR = 0.2, 95% CI = .1–.4).

Conclusions.—Over a decade, numbers of JORRP case-patients and incidences declined significantly. Incidences calculated using national denominator data are likely underestimates;

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those calculated using state-level denominator data could be overestimates. These declines are most likely due to HPV vaccination. Increasing vaccination uptake could lead to elimination of this HPV-related disease.

Keywords

recurrent respiratory papillomatosis; human papillomavirus (HPV); papillomavirus infections; papillomavirus vaccines; child health

Juvenile-onset recurrent respiratory papillomatosis (JORRP) is a serious pediatric disease characterized by recurrent growth of papillomas in the larynx or elsewhere in the respiratory tract [1]. Although rare, it is believed to be the most common benign neoplasm of the larynx in young children [2]. Distal spread to the lower respiratory tract and frequency of required surgical intervention are the criteria commonly used to assess severity of disease [3]. JORRP is usually caused by low-risk human papillomavirus (HPV) types 6 or 11, which are also the most common cause of anogenital warts. Causative HPV infection is presumably transmitted vertically during vaginal delivery.

The primary modality for management of JORRP is surgical removal by a pediatric otolaryngologist [2]. These physicians are highly specialized; the American Society of Pediatric Otolaryngology has fewer than 600 active US members, most of whom practice in large urban areas [4]. Repeated surgeries may be needed to maintain a patent airway and to preserve voice function. Some children require 4 or more surgeries per year, but disease course can be highly variable [5].

HPV vaccination can prevent new infections with the types of HPV that cause JORRP [6]. To date, nearly all adolescents and young adults who have been vaccinated in the United States received either quadrivalent HPV vaccine (Gardasil, Merck & Co.), introduced in 2006, or 9-valent HPV vaccine (Gardasil 9, Merck & Co.), introduced in late 2015; both of these vaccines protect against HPV types 6 and 11 as well as certain oncogenic HPV types [6, 7]. These vaccines are highly immunogenic and have excellent safety profiles [8, 9]. The Advisory Committee on Immunization Practices (ACIP) recommends routine HPV vaccination for all US adolescents at age 11 or 12 years (or can be given starting at age 9 years) [6, 7, 10]. Catch-up vaccination is recommended through age 26 years [11]. For unvaccinated adults ages 27 through 45 years, shared clinical decision making between a patient and their physician regarding HPV vaccination is recommended [11].

As HPV vaccination coverage increases, early impacts are being identified. Between 2006, when HPV vaccination was first recommended, and 2019, coverage increased among US adolescents aged 13–17 years to an estimated 73.2% with ≥1 dose and 56.8% up to date for the series among females, and 69.8% with ≥1 dose and 51.8% up to date for the series among males [12]. In the United States, significant declines have been observed in the prevalence of infections with vaccine-type HPV [13–15], as well as declines in resulting disease outcomes including anogenital warts [16] and cervical precancers [15]. Because the HPV types that cause JORRP (ie, HPV types 6 and 11) are vaccine-preventable, vertical transmission of these HPV types and thus the incidence of JORRP also might be reduced by the US HPV vaccination program [17].

JORRP is not currently a nationally notifiable condition in the United States, and national data on incidence and prevalence are lacking [18]. Trends in JORRP incidence in the United States have not been assessed in the HPV vaccine era. To monitor the burden of JORRP and assess the potential impact of HPV vaccination in the United States, we established a study to track incident and prevalent cases. The objective of this analysis is to assess trends in JORRP cases before and after HPV vaccine introduction in the United States.

METHODS

In 2015, we established a multicenter study to enroll a convenience sample of case-patients aged <18 years who presented for care of previously or newly diagnosed JORRP at the participating pediatric otolaryngology practices of tertiary medical care centers in the United States. The prospective cross-sectional component of the study enrolled participants beginning in 2015 and included collection of demographic and clinical information from medical records, as well as collection of papilloma specimens for HPV typing and maternal survey questions, as we reported elsewhere [19]. In addition, we collected retrospective data about JORRP case-patients at the same clinical centers by searching the electronic medical record (EMR) using a list of suggested ICD-9 codes (before 2015), ICD-10 codes (2015–present), and CPT procedure codes (ICD-9 codes: 210.6, 210.7, 210.80, 212.1 (laryngeal papilloma), 212.2 (tracheal papilloma), 212.3, 478.79; ICD-10 codes: D10.5, D10.6, D10.7, D10.9, D14.1 (benign neoplasm of larynx), D14.2, D14.3, D14.4; CPT Procedure codes: 30.09 (laryngeal excision), 31.42 (laryngoscopy), 31.43 (biopsy of larynx), 31.44, 31.5, 31.74, 31.92, 32.01, 33.21, 33.23). After chart review of each medical record to confirm the diagnosis of JORRP, information on demographics and clinical characteristics was abstracted from eligible medical records.

To assess numbers of JORRP case-patients over time with a stable prevaccine era baseline, both retrospective and prospective cross-sectional data collection were used to identify JORRP case-patients who were born during 2004–2013 (Figure 1). This date range was selected to include years with the most complete data collection at the participating centers; the earliest year by which all centers reported a JORRP case-patient visit was 2008, and the latest year for which all centers contributed visit data was 2017. To determine birth years to include in this analysis, we used the median age at JORRP diagnosis (age 4 years) in our overall data set, which included all case-patients enrolled in the prospective cross-sectional component and all case-patients identified in the retrospective component of the study, based on the assumption that birth year was when each JORRP case-patient acquired their causative HPV infection and that it would take an average of 4 years to JORRP diagnosis. For this reason, the analytic period included birth years from 2004 through 2013, beginning 4 years before the earliest consistent date of data retrieval in 2008, and ending 4 years before the most recent completed data collection in 2017.

To calculate JORRP incidence, we used denominators from vital statistics on annual number of births, considering both US national and state-level natality data from each state where participating centers were located [20]. In 2 similar methodologic approaches, JORRP incidence rate ratios (IRR) and 95% confidence intervals (CI) were calculated over 2-year intervals for stability, where the numerator was the number of JORRP case-patients by year

of birth, and the denominator was either national or state-level number of births. Data were analyzed using Poisson regression, accounting for dispersion, to compare the earliest 2-year interval and the most recent 2-year interval.

RESULTS

This analysis included data collected from the pediatric otolaryngology practices of 26 tertiary medical centers in 23 US states (Figure 2). We identified 576 JORRP case-patients born in 2004–2013 (Table 1). Among this group, similar proportions were male and female. By race/ethnicity, the largest group was non-Hispanic white, with various race/ethnicities represented. Median age at JORRP diagnosis was 3.4 years (interquartile range: 1.9, 5.5 years); 55.9% of children received their diagnosis before age 4 years.

The number of identified JORRP case-patients was 165 among children born in 2004–2005, before HPV vaccine introduction, and 167 among children born in 2006–2007, when mothers were unlikely to have been vaccinated before their pregnancy. Numbers declined in each subsequent 2-year birth interval; there were 36 JORRP case-patients identified among children born in 2012–2013 (Figure 3). Incidence of JORRP using national denominator data declined significantly from 2.0 cases per 100 000 births in 2004–2005 to 0.5 cases in 2012–2013 (IRR = 0.2, 95% CI = .1–.4). Incidence of JORRP using state-level denominator data declined significantly from 2.9 cases per 100 000 births in 2004–2005 to 0.7 cases in 2012–2013 (IRR = 0.2, 95% CI = .1–.4).

DISCUSSION

In this multi-center study conducted at pediatric otolaryngology practices in the United States, we found that JORRP incidence was significantly lower among children born in the years following HPV vaccine introduction in 2006. Over a decade, numbers of JORRP case-patients and incidences declined significantly, with an IRR of 0.2 comparing births in 2012–2013 to those in 2004–2005. These declines are most likely due to HPV vaccination.

Findings from the prospective cross-sectional component of our study, reported elsewhere, showed that US children with JORRP were commonly first-born children delivered vaginally to young mothers who reported no receipt of HPV vaccination before delivery; [19] these epidemiologic features have been identified as the “JORRP triad” [21]. In addition, vaccine-preventable HPV types were detected in 94.7% of respiratory papilloma specimens tested [19].

During the prevaccine era, a small number of studies aimed to assess burden of JORRP in the United States. A registry with 22 participating pediatric otolaryngology centers throughout the United States collected clinical information about 603 children aged <18 years with JORRP seen between 1996 and 2002, but this study did not identify population denominators or assess incidence [22, 23]. A survey conducted in 1993 of board-certified otolaryngologists practicing in the United States estimated that JORRP incidence was 4.3 per 100 000 children aged <14 years [24]. A population-based study conducted in 1996 in 2 US cities reported that JORRP incidence was 0.36–1.11 per 100 000 children aged <18 years [25]. An analysis of health insurance claims data from 2006 in 2 commercial databases

estimated that JORRP incidence was 0.51 per 100 000 privately insured and 1.03 per 100 000 publicly insured children aged <18 years [26]. Unlike these previous studies, our study assessed incidence by birth cohort. Incidence rates in previously published studies cannot be directly compared due to differing study methodologies.

JORRP is one of several HPV-attributable morbidities. Outcomes due to oncogenic HPV types account for most of the disease burden due to HPV, with the most common HPV-attributable cancers being cervical cancer in women and oropharyngeal cancer in men [27]. Although JORRP is rare, changes in quality of life for affected children and their families as well as economic burden are substantial. Lower health-related quality of life has been reported among children affected by JORRP compared to unaffected controls [28, 29]. Annual direct medical costs of treating JORRP in the United States in 2004–2007 were estimated to be $123 000 000, with a range of $6 000 000 to $604 000 000 in 2010 US dollars [30]. Per case, medical treatment costs were estimated to be $149 000 in 2018 [31].

Our findings are subject to several important limitations. First, these data are not complete for the United States, nor are they nationally representative, although they do include a large number of clinical centers where pediatric otolaryngologists practice across the United States. Given referral patterns for JORRP, it can be assumed that essentially all children with JORRP in these catchment areas would be seen by the participating practices. Although not typical of this disease, there could be some children with JORRP managed outside the tertiary care medical centers in this 23-state study. Second, our incidence estimates were based on imprecise data, and we used 2 different denominator estimates. Because case ascertainment was not complete for the entire United States, incidences calculated using national denominator data are likely underestimates. Further, since the catchment area for the participating centers was not limited to the states where the centers were located, incidences calculated using state-level denominator data could be overestimates due to out-of-state referrals. True incidence is likely between these two estimates. Third, we cannot rule out the possibility of other cohort effects, although HPV vaccination is the most likely explanation for the decrease in HPV-related disease in this time frame.

Worldwide, population-level impacts of HPV vaccination programs have been demonstrated, including significant reductions in HPV infections, anogenital warts, and cervical precancers [32]. Declines in JORRP also followed the 2007 introduction of HPV vaccine in Australia, a country in which high, sustained vaccination coverage was achieved; number of incident JORRP cases reported in Australia fell from 7 in 2012 to 1 in 2016 and 2 in 2017, and none were reported in either 2018 or 2019 [33, 34]. In countries with HPV vaccination programs, a national registry or database may allow assessment of HPV vaccine impact on RRP [35]. In Canada, for example, a national database of children with JORRP will also allow for monitoring the effect of increasing HPV vaccination coverage on JORRP incidence over time [36].

Declines in JORRP following HPV vaccine introduction in the United States likely demonstrate the impact of HPV vaccination. Increasing vaccination uptake could lead to elimination of this rare but serious HPV-related disease among children in the United States.

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Potential conflicts of interest.

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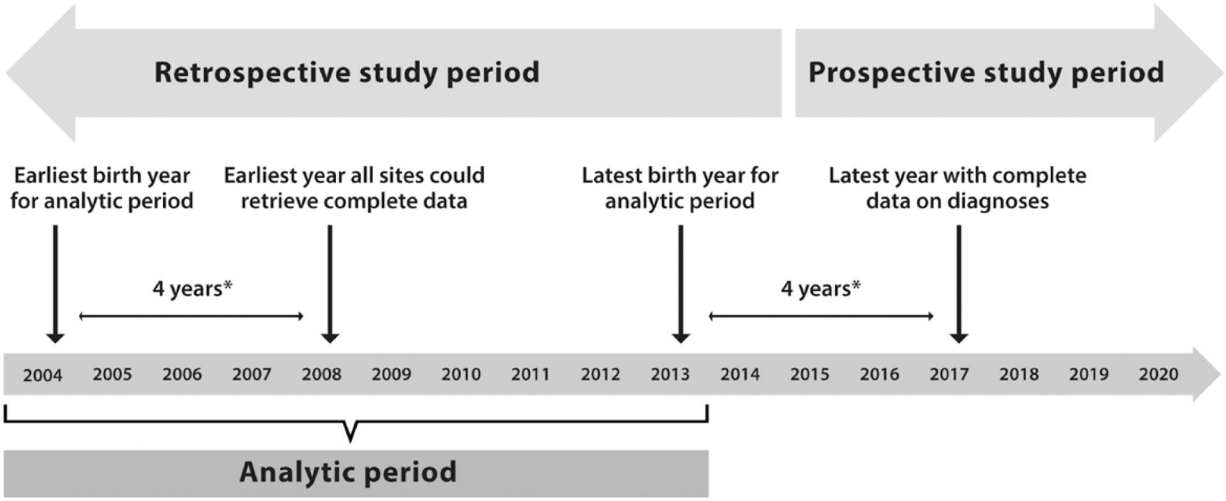


Figure 1.

Study periods and birth years of US children with juvenile-onset recurrent respiratory papillomatosis (JORRP) included in analytic period. Abbreviation: HPV, human papillomavirus. *Median age at JORRP diagnosis in our overall dataset (age 4 years) was used to determine birth years from enrollment data, based on the assumption that birth year was when each JORRP case-patient acquired their causative HPV infection. The analytic period included birth years from 2004 through 2013, beginning 4 years before the earliest consistent date of data retrieval in 2008, and ending 4 years before the most recent completed data collection in 2017.

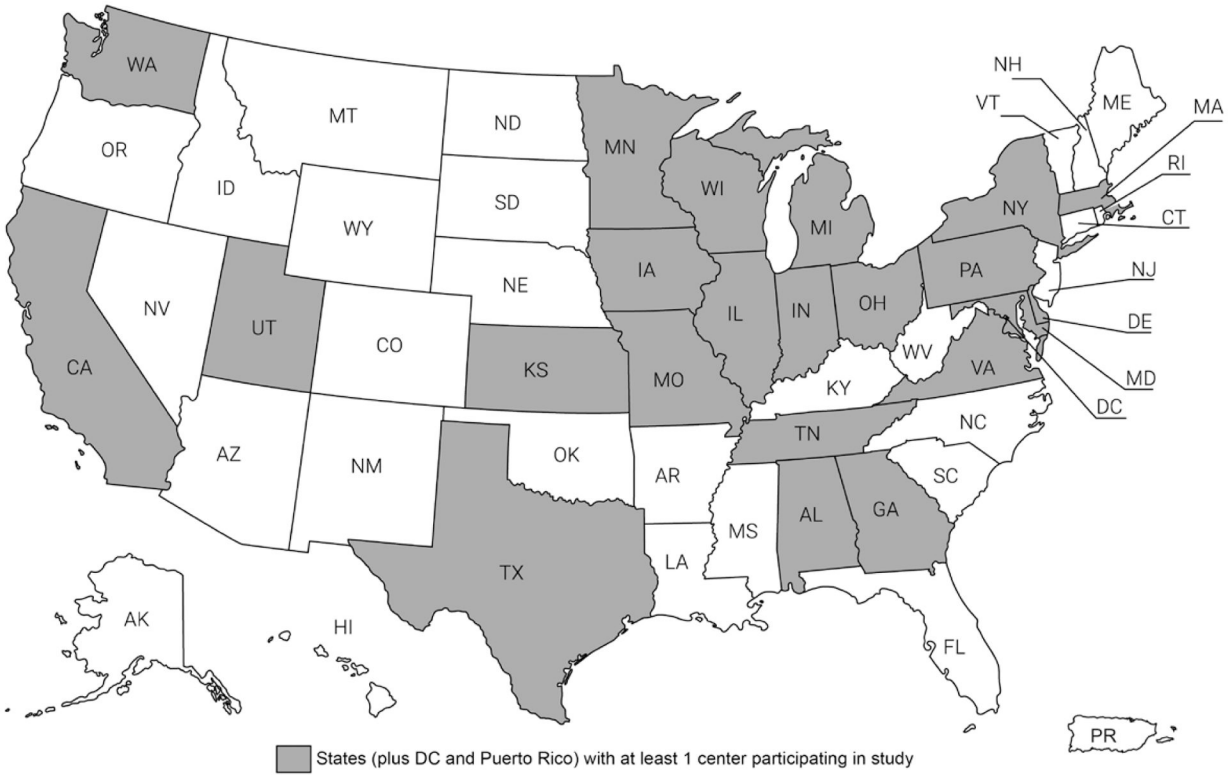
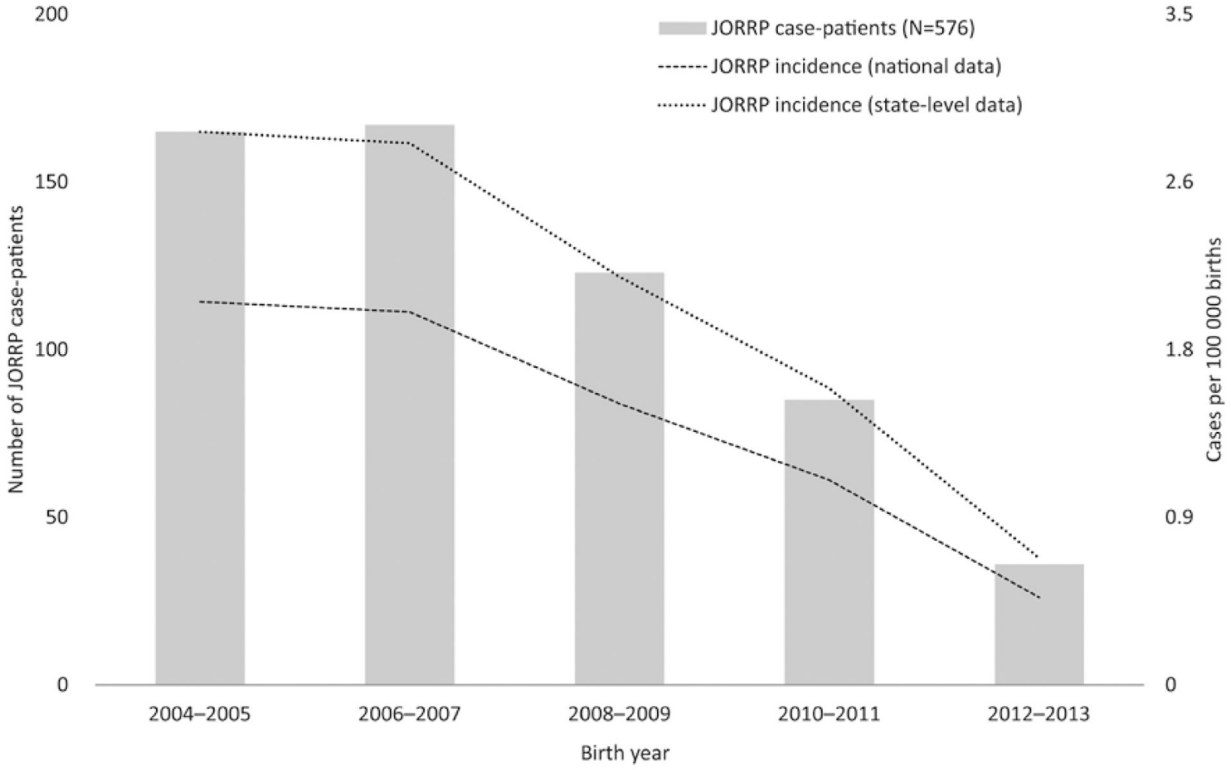


Figure 2.

States with at least 1 medical center participating in the juvenile-onset recurrent respiratory papillomatosis (JORRP) monitoring study.



Birth years	Number of JORRP cases	Incidence per 100 000 births	
		National denominator data	State-level denominator data
2004–2005	165	2.0	2.9
2006–2007	167	1.9	2.8
2008–2009	123	1.5	2.1
2010–2011	85	1.1	1.5
2012–2013	36	0.5	0.7

Figure 3.

Juvenile-onset recurrent respiratory papillomatosis (JORRP) case-patients by birth year and incidence based on US national or state-level denominator data.

Table 1.

Characteristics of US Children With Juvenile-onset Recurrent Respiratory Papillomatosis (JORRP) Born During 2004–2013

Characteristic	n (%)
Total	576 (100)
Sex	
Male	292 (50.7)
Female	282 (49.0)
Unknown/missing	2 (0.3)
Race/ethnicity	
Non-Hispanic white	270 (46.9)
Non-Hispanic black	127 (22.1)
Hispanic	93 (16.2)
Non-Hispanic Asian/Pacific Islander	5 (0.9)
Non-Hispanic mixed race or other race	28 (4.9)
Unknown/missing	53 (9.2)
Age at JORRP diagnosis	
Median (IQR), y	3.4 (1.9, 5.5)
Age at JORRP diagnosis	
<4 y	322 (55.9)
4–8 y	211 (36.6)
9–13 y	28 (4.9)
Unknown/missing	15 (2.6)

Abbreviation: IQR, interquartile range.