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Juvenile-Onset Recurrent Respiratory Papillomatosis in the United States, Epidemiology and HPV Types—2015–2020

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Abstract

Background.—Juvenile-onset recurrent respiratory papillomatosis (JORRP) is a rare disease characterized by the growth of papillomas in the respiratory tract. In the United States, JORRP is not a nationally notifiable condition and current data are limited.

Methods.—Children with JORRP aged <18 years were enrolled from 26 pediatric otolaryngology centers in 23 US states from January 2015 through August 2020. Demographic, birth information, and maternal vaccination history were collected from a parent/guardian. Clinical history was abstracted from medical records. Papilloma biopsies were tested for 28 human papillomavirus (HPV) types. Mothers who delivered in 2006 or later were considered age-eligible for HPV vaccination if aged ≥26 years in 2006. We described characteristics of enrolled children and their birth mothers and analyzed disease severity by diagnosis age and HPV type using multiple logistic regression.

Results.—Among 215 children with JORRP, 88.8% were delivered vaginally; 64.2% were firstborn. Among 190 mothers, the median delivery age was 22 years. Among 114 (60.0%) age-eligible for HPV vaccination, 16 (14.0%) were vaccinated, 1 (0.9%) before delivery. Among 162 specimens tested, 157 (96.9%) had detectable HPV; all 157 had a vaccine-preventable type. Disease severity was associated with younger diagnosis age and HPV 11; adjusted analyses found only younger diagnosis age significant (adjusted odds ratio: 6.1; 95% confidence interval: 2.9, 12.8).

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Conclusions.—Children with JORRP were commonly firstborn and delivered vaginally to young mothers; most of the mothers reported no HPV vaccination before delivery. Vaccine-preventable HPV was identified in all specimens with detectable HPV. Increasing preexposure HPV vaccination could substantially reduce or eliminate JORRP in the United States.

Keywords

child; human papillomavirus 6; human papillomavirus 11; laryngeal neoplasms; recurrent respiratory papillomatosis

Recurrent respiratory papillomatosis (RRP) is a rare and serious condition in which wart-like lesions repeatedly grow in the respiratory tract [1]. It is usually benign, although malignant transformation can occur. When RRP onset occurs during childhood, it is referred to as juvenile-onset RRP (JORRP) [2]. RRP is caused by infection with human papillomavirus (HPV), usually types 6 or 11, which also cause almost all anogenital warts [3]. In children with JORRP, HPV is presumably acquired through vertical transmission [2].

JORRP has a substantial impact on affected children and their families and caregivers. Treatment consists of surgical removal of papillomas to clear the airway, and in some cases, adjuvant therapy is used concurrently [4]. In particularly aggressive cases, tracheotomy may be required [5]. By convention, disease severity or aggressiveness has been based on the number of annual and/or lifetime surgeries, distal spread, or a composite of the 3 [6]. Several prior studies have assessed the relationship between disease severity and HPV type and/or age at diagnosis [7–20]. Costs to treat the disease are high; in 2018, lifetime cost per case of JORRP in the United States was estimated to be \$149 000 [21].

Quadrivalent HPV vaccine (4vHPV, Gardasil, Merck & Co.) and 9-valent HPV vaccine (9vHPV, Gardasil 9, Merck & Co.), introduced in 2006 and 2015, respectively, protect against infections with HPV types 6 and 11. 4vHPV also protects against oncogenic types 16 and 18, and 9vHPV also protects against oncogenic types 16, 18, 31, 33, 45, 52, and 58. In the United States, routine HPV vaccination has been recommended for females since 2006 and males since 2011. HPV vaccination is recommended at the age of 11 or 12 years (or can start at the age of 9 years); catch-up vaccination is recommended for all persons through the age of 26 years, with shared clinical decision-making for some adults aged 27 through 45 years [22, 23].

JORRP is not a nationally notifiable condition in the United States; therefore, data are limited regarding demographic and clinical characteristics and type-specific HPV infections of children with JORRP. Most available HPV typing data for US children with JORRP are from single-site studies [12, 16, 19, 24]. In a recent study of 339 children with JORRP from 8 countries, many were from the United States, but US data were not presented separately [8].

We conducted a multi-center observational study to assess the current epidemiology of children with JORRP in the United States and to monitor the potential impact of HPV vaccination in the United States. The objectives of this analysis were to describe

demographic and clinical characteristics of US children with JORRP and their birth mothers, evaluate HPV types, and describe disease severity.

METHODS

We enrolled participants in a cross-sectional study from pediatric otolaryngology centers at major medical institutions in the United States. Centers were identified and contacted for enrollment in collaboration with the national RRP Task Force. Locations of centers were mapped according to the US Department of Health and Human Services (HHS) regions [25]. From these centers, we included all children diagnosed with JORRP before the age of 18 years who presented for clinical care from January 2015 through August 2020. Study participants were incident cases (enrolled within 12 months of diagnosis) or prevalent cases (enrolled 12 months after diagnosis). Siblings were not excluded. Written informed consent was obtained from a parent/guardian for all study participants. The study protocol was reviewed and approved by institutional review boards at each participating institution and at the Centers for Disease Control and Prevention (CDC).

Three standardized data collection instruments were used. During the study visit, the parent/guardian completed a questionnaire regarding demographic information about the child with JORRP (eg, age, sex, race/ethnicity, and birth order) and a questionnaire regarding a birth mother's health and medical information relevant to the birth of her child with JORRP (eg, delivery course, history of anogenital warts or abnormal cervical cancer screening test result, and timing of HPV vaccination). A medical record abstraction form was completed by center research staff regarding clinical information about the child with JORRP using electronic health records (eg, symptoms, anatomic sites involved, comorbidities, and medical and surgical management).

Biopsy specimens (ie, small fragments of papillomas) were collected from children undergoing clinically indicated surgical debulking of their respiratory papilloma lesions. Specimens were stored at -20°C prior to shipment to CDC on dry ice. Tissues were digested with proteinase K and extracted with QIAamp (Qiagen, Germantown, Maryland). The 200 μL extract was stored at -20°C until testing with Novaplex II HPV28 (Seegene Technologies, Walnut Creek, California) following the manufacturer's guidelines. Type-specific results were evaluated for 28 HPV types (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 66, 68, 69, 70, 73, or 82) and internal controls. A specimen was considered sufficient for analysis if results were positive for at least 1 HPV type or internal control.

Descriptive statistics were calculated, including count and percentage for categorical variables and median and interquartile range (IQR) for continuous variables. Births occurring at <37 weeks of gestation were considered preterm; 37 to <39 weeks early term, 39 to <41 weeks full term, 41 to <42 weeks late term, and ≥ 42 weeks post-term [26]. Date of HPV vaccination was considered valid for study purposes beginning in 2006 when HPV vaccines were first licensed [22]. Mothers who delivered in 2006 or later were considered age-eligible for HPV vaccination before giving birth if the mother was aged 26 years or younger in 2006. For mothers, history of HPV vaccination was self-reported; for

children with JORRP, history of HPV vaccination was obtained from their medical records. Age at vaccination was based on medical record date, if available. Age at vaccination was classified as younger than 9 years either by medical record date or history of vaccination at the time of enrollment, if age at enrollment was younger than 9 years and vaccination date was not available from the medical record. Severe disease was defined as 1 of the following: 10 lifetime surgeries, 4 surgeries in the past 12 months, and/or distal spread of papillomas. Disease severity was analyzed by HPV type (HPV 6 vs HPV 11) and by age at diagnosis (age 4 years vs age >4 years). For analysis of stratified data, chi-square or Fisher's exact test were used for categorical variables and Mann-Whitney-Wilcoxon test for continuous variables. Variables with a *P*-value of <.05 were considered significant. To assess relationships between HPV type and age at diagnosis with disease severity, we used logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI) and multiple logistic regression, adjusting for both variables to calculate adjusted odds ratios (aOR). All calculations were performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

From January 2015 through August 2020, 26 medical centers in 23 US states located in all 10 HHS regions (Figure 1) participated and enrolled 215 children with JORRP, including 1 set of twins (Table 1). Maternal information was available for 190 birth mothers. Among the 215 enrolled children, 61 (28.4%) were enrolled within 12 months of their JORRP diagnosis and 144 (67.0%) were enrolled 12 months. The median age at JORRP diagnosis was 4.5 years (IQR: 2.3, 6.4) and 115 (53.5%) were male. Regarding race/ethnicity, 108 children (50.2%) were non-Hispanic White, 47 (21.9%) were Hispanic, 46 (21.4%) were non-Hispanic Black, 10 (4.7%) were multiracial, and 2 (0.9%) were Asian. Most were delivered vaginally (191, 88.8%) and were firstborn (138, 64.2%).

Among 190 birth mothers of children with JORRP, 169 (90.0%) were born in the United States, and the median maternal age at delivery was 22 years (IQR: 19, 27) (Table 1). Most of the mothers (114, 60.0%) were age-eligible for HPV vaccination at the time of delivery. Among these 114 age-eligible mothers, only 1 (0.9%) self-reported receiving HPV vaccination before delivery (at age 26 years), 6 (5.3%) reported vaccination after delivery, and 9 (7.9%) did not know the timing of their vaccination relative to delivery; 83 (72.8%) reported no vaccination before delivery, and 15 (13.2%) were unsure about their vaccination history. Among all mothers, 110 (57.9%) reported a history of cervical cancer screening and 36 (19.0%) reported a history of anogenital warts; among these 36, 24 (66.7%) had anogenital warts present at the time of delivery.

Among children with JORRP, the most common presenting symptoms were hoarseness (94.9%) and voice change (71.2%) (Table 2). Papillomas were most commonly documented in the larynx (93.5%), and most had papillomas only at one site (77.7%). Comorbidities included asthma (12.1%) and gastroesophageal reflux disease (9.8%). The median number of lifetime surgeries was 6 (IQR: 3, 16), and the median number of surgeries in the past 12 months was 2 (IQR: 1, 3). Nine children (4.2%) had a history of tracheotomy and 67 (31.2%) had received adjuvant therapy. Among children treated with adjuvant therapy, the

most common therapy was cidofovir (47, 70.2%). Thirty-two children (14.9%) had received HPV vaccination, including 7 children who were vaccinated before the age of 9 years.

A total of 162 papilloma specimens were sufficient for HPV DNA detection (Figure 2). HPV was detected in 157 (96.9%) specimens. Of these 157 specimens, 155 (95.6%) had only 1 HPV type detected. Most of the specimens had HPV 6 only (129, 79.6%) or HPV 11 only (25, 15.4%); 1 specimen had HPV 16 only. In the remaining 2 specimens (1.2%), 2 different HPV types were detected: 1 with HPV 6 and 44, and 1 with HPV 6 and 54. All 157 specimens with detectable HPV had at least 1 vaccine-preventable HPV type.

To evaluate disease severity by HPV type, analysis was limited to the 156 children with HPV 6 or 11 detected in their papilloma specimens: 131 (83.9%) with HPV 6 and 25 (16.0%) with HPV 11 (Table 3). Compared with children with HPV 6, a higher percentage of children with HPV 11 had severe disease (76.0% vs 44.3%; $P < .01$), including more with papillomas in the lower respiratory tract (24.0% vs 8.4%; $P = .03$), more lifetime surgeries (median: 12 [IQR: 4, 38] vs 6 [IQR: 3, 13]; $P = .03$), and more surgeries in the past 12 months (median: 3 [IQR: 2, 5] vs 2 [IQR: 1, 3]; $P < .01$). Median age at JORRP diagnosis was younger for children with HPV 11 than for children with HPV 6 (median: 2.2 years [IQR: 1.5, 3.5] vs 4.7 years [IQR: 2.7, 7.1]; $P < .01$).

To evaluate disease severity by age at JORRP diagnosis, analysis was limited to the 207 children for whom age at diagnosis was available (Table 4). A higher percentage of children diagnosed with JORRP at age <4 years had severe disease compared with children diagnosed at age >4 years (70.1% vs 30.9%, $P < .01$), including more with papillomas in the lower respiratory tract (17.5% vs 6.4%; $P = .01$), more lifetime surgeries (median: 13 [IQR: 6, 26] vs 4 [IQR: 2, 8]; $P < .01$), and more surgeries in the past 12 months (median: 2 [IQR: 1, 4] vs 2 [IQR: 1, 3]; $P < .01$). In both groups, the majority had HPV 6; however, compared with children diagnosed at age >4 years, those diagnosed at age ≤ 4 years were less likely to have HPV 6 (73.6% vs 90.2%, $P < .01$) and more likely to have HPV 11 (25.0% vs 4.9%; $P < .01$).

Logistic regression was conducted to further assess associations between HPV type and age at diagnosis with disease severity. Unadjusted ORs were consistent with stratified analysis, with HPV 11 and younger age at diagnosis both significantly associated with severity (HPV 11 OR: 4.2, 95% CI: 1.5, 12.0; diagnosed at age ≤ 4 years OR: 7.0, 95% CI: 3.4, 14.3). Adjusted analyses found that younger age at diagnosis remained significantly associated with severity (aOR: 6.1, 95% CI: 2.9, 12.8).

DISCUSSION

This study of 215 children with JORRP enrolled from pediatric otolaryngology centers in the United States from January 2015 through August 2020 reports demographic and clinical characteristics, information about birth mothers, and HPV types detected in papilloma biopsy specimens. We found that among US children with JORRP, 64% were firstborn, 89% were delivered vaginally, and their birth mothers delivered at a median age of 22 years. By comparison, in the United States overall in 2018, 68% of children were delivered

vaginally and first-time mothers delivered at a mean age of 27 years [27]. Our findings are consistent with literature describing the “JORRP triad” of characteristics associated with the disease: a firstborn child, a vaginal delivery, and a young mother [28, 29]. In our study, a small percentage of children with JORRP were delivered via cesarean section, suggesting that cesarean section does not eliminate the possibility of vertical transmission [9, 29]. Importantly, only one mother reported HPV vaccination before delivery, even though the majority of mothers were age-eligible for routine or catch-up HPV vaccination as recommended in the United States since 2006.

Vaccine-preventable HPV was detected in papilloma biopsy specimens from almost all children with JORRP: HPV 6 in 83.9% and HPV 11 in 16.0%. Similarly, high prevalence of HPV 6 and 11 was reported by other studies of JORRP conducted around the world [9–12, 19, 24, 30, 31]. Since the causative HPV infection is presumably acquired through vertical transmission, the high proportion of vaccine-preventable HPV types among children with JORRP suggests that the majority of cases could have been prevented by prophylactic vaccination of their mothers as adolescents, before exposure to HPV during sex [5, 32]. HPV vaccination is highly effective for prevention of vaccine-targeted HPV infection.[22]

Previous studies have assessed characteristics of children with JORRP. In the United States, a registry collected data from multiple sites between 1996 and 2002 [17] while other studies were conducted at 1 or 2 sites: a retrospective study from 1984 to 1994 [24], a 10-year prospective study beginning in 1993 [19], and a 2-site study conducted from 1996 to 1997 [33]. Similar to our findings, most reported slightly more males than females with JORRP [17, 19, 33] and most children with JORRP were White [17, 19, 24, 33]. Age at diagnosis varied across US studies, from 2.8 to 4.6 years [17, 19, 24, 33]; our study found a median age at diagnosis of 4.5 years, similar to a Canadian retrospective registry-based study of cases from 1994 to 2007 and an Australian surveillance study conducted from 2011 to 2016, which reported medians of 4.4 [9] and 4.0 years [30], respectively. Also similar to our findings, most reported a high proportion of cases with laryngeal papillomas [9, 17]. The earlier US registry reported a median number of 13 lifetime surgeries [17], higher than the median number found in our study, 6, and in the Canadian registry, 7 [9]. Recent studies have described various adjuvant therapies being used for JORRP [4, 5], including cidofovir as one of the most common, also similar to our findings. Some physicians offer HPV vaccination to children with JORRP before the routinely recommended age, based on small observational studies suggesting longer inter-surgical intervals and occasional remissions after vaccination [34]. In our study, we found that 7 children with JORRP received HPV vaccination before the age of 9 years. Of note, our study was not designed to provide data on HPV vaccination for the treatment of JORRP or prevention of recurrent disease. There have been no randomized clinical trials of HPV vaccination as a potential treatment for JORRP; HPV vaccination has not been found to prevent the progression of infection to disease, enhance clearance of infection, or treat cervical disease [35]. Some data have suggested that HPV vaccination after treatment for cervical disease might reduce recurrence; further studies are ongoing [36].

Younger age at diagnosis and infection with HPV 11 were both significantly associated with more severe disease among children with JORRP in our study. Previous studies conducted

in the United States and internationally found that younger age at diagnosis was associated with severe disease [7–9, 17–19], defined as a higher average number of surgeries per year or a composite variable, as we used. Although one study concluded that HPV 6 was associated with more severe disease [14] and another concluded that HPV type was not associated with severity [15], most of the studies found that children with HPV 11 had more aggressive disease [10, 12, 16, 19]. Three studies assessed this relationship through modeling and found that age at diagnosis was the only significant predictor of disease severity when controlling for HPV type, similar to our findings [11, 13, 20].

Our findings are subject to at least 3 limitations. First, although we included 26 centers from multiple states in various US regions, we did not collect data from all US states or medical centers that might care for children with JORRP; thus, the generalizability of our findings might be limited. The American Society of Pediatric Otolaryngology suggests that at least 100 different pediatric ear, nose, and throat centers provide clinical services in the United States [37], however that includes small offices as well as large medical institutions, and it is reasonable to expect that most children with JORRP would receive care at major medical centers such as those participating in our study. Second, information about enrolled children was collected at a single visit without a longitudinal component or additional follow-up. Since both incident and prevalent cases were enrolled, length of available clinical history varied; age and disease stage at the time of enrollment would affect clinical information on number of lifetime and recent surgeries, adjuvant therapies received, history of tracheotomy, and location of papillomas. Third, not all birth mothers were available, and reported maternal characteristics could have been subject to recall bias, limiting the ability to determine maternal HPV vaccination history and maternal HPV exposure prior to vaccination.

Our findings contribute to literature regarding characteristics of children with JORRP and suggest that prevention of this disease is possible in the HPV vaccine era. Already, reductions in early HPV-associated outcomes including prevalence of HPV infection, anogenital warts, and cervical precancers have been reported after the introduction of national HPV vaccination programs [38]. Australia was the first country to show a decline in JORRP incidence, following the implementation of a national HPV vaccination program that achieved rapid and high vaccination coverage in target and catch-up age groups [30], and, recently, declining trends in JORRP incidence were reported in the United States using data collected through this study [39]. HPV vaccination coverage has been increasing in the United States; in 2019, 1-dose coverage was 73% among 13- to 17-year-old females and 70% among 13- to 17-year-old males [40]. Since vaccine-preventable HPV types cause JORRP and causative HPV infections are presumed to be vertically transmitted [2], providing preexposure HPV vaccination as recommended to all adolescents could reduce or eliminate JORRP in the United States.

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Potential conflicts of interest.

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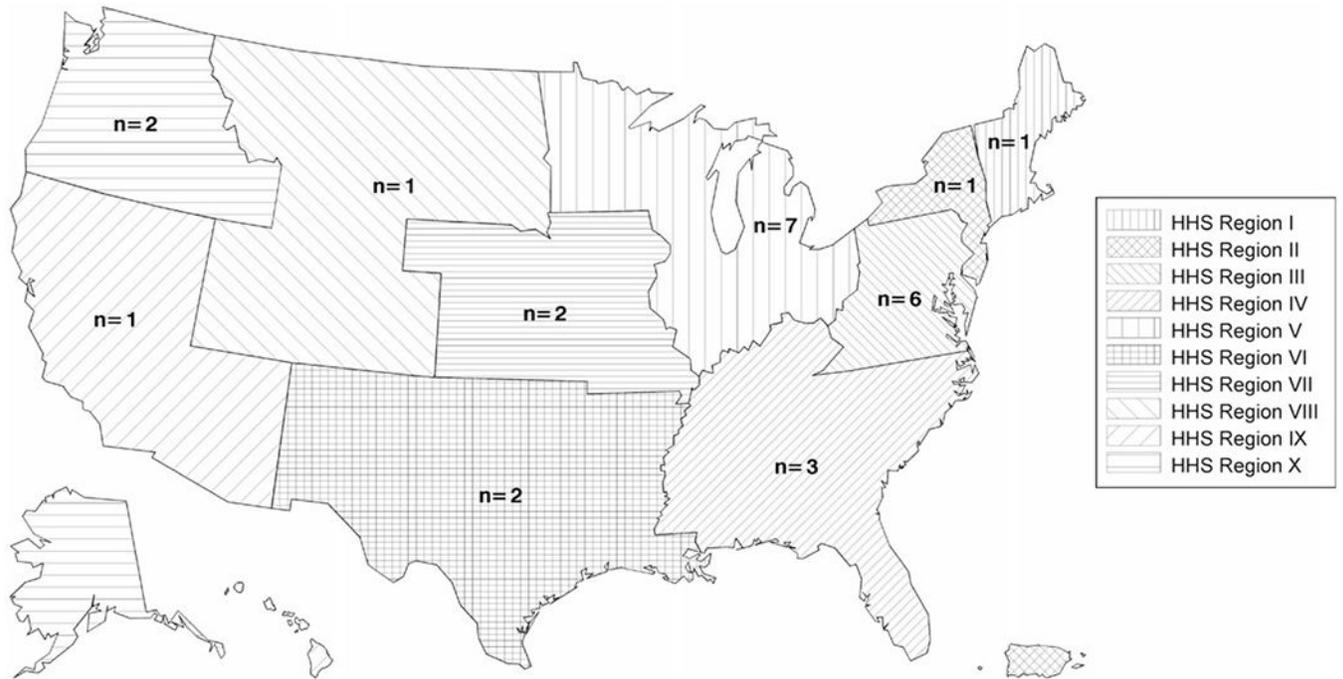


Figure 1. Number of participating pediatric otolaryngology centers, by US Department of Health and Human Services region—United States, 2015–2020.

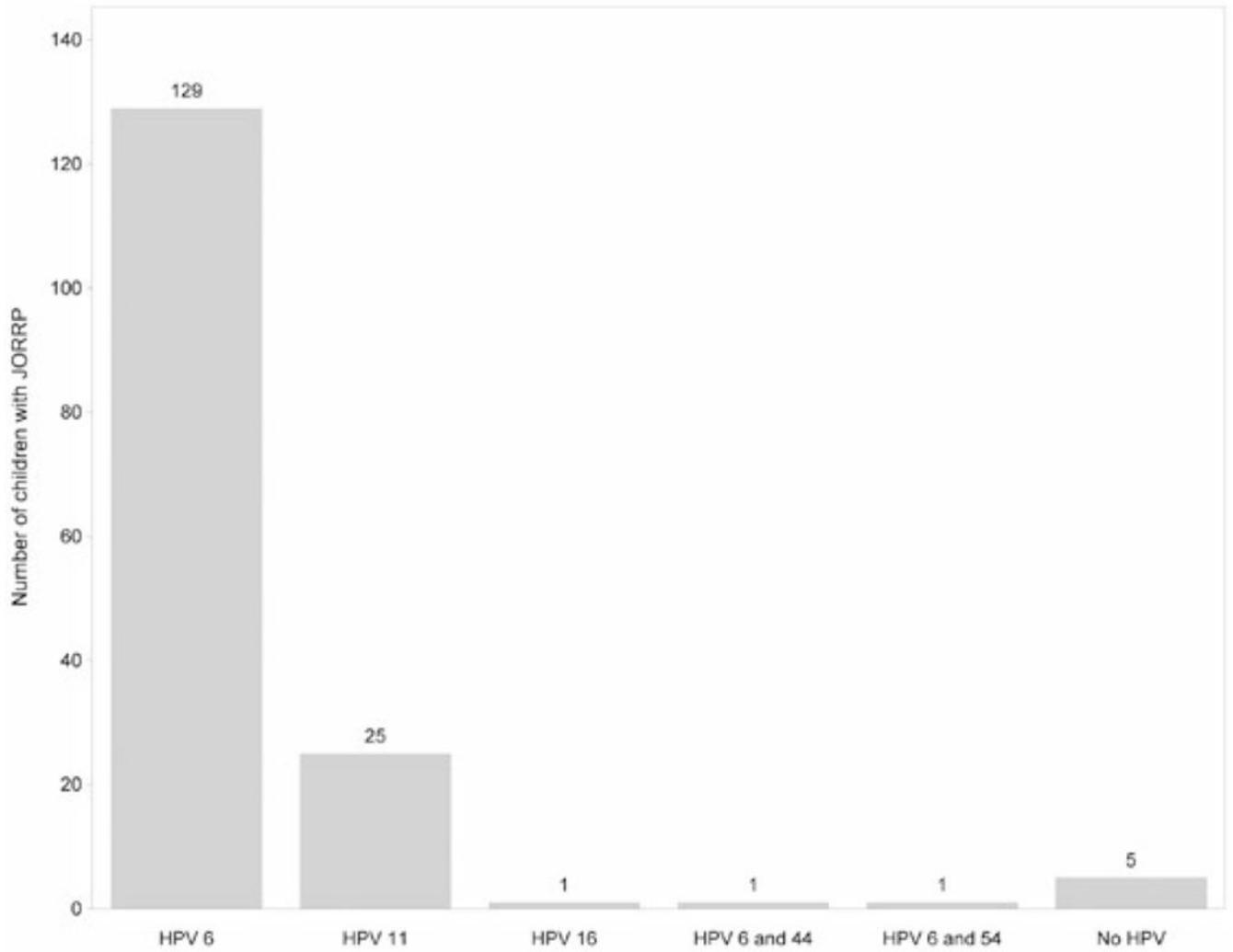


Figure 2. Human papillomavirus (HPV) types detected in papilloma biopsy specimens (N = 162) from children with juvenile-onset recurrent respiratory papillomatosis (JORRP)— United States, 2015–2020.

Table 1.

Demographic and Other Characteristics of Children with Juvenile-Onset Recurrent Respiratory Papillomatosis (JORRP) and their Birth Mothers—United States, 2015–2020

Characteristic	n	% or median (IQR)
Children with JORRP (N = 215)		
Age at JORRP diagnosis, y	207	4.5 (2.3, 6.4)
Age at study enrollment, y	213	8 (5, 12)
Sex		
Male	115	53.5
Female	98	45.6
Unknown	2	0.9
Race/ethnicity		
Non-Hispanic White	108	50.2
Hispanic	47	21.9
Non-Hispanic Black	46	21.4
Non-Hispanic multiracial	10	4.7
Non-Hispanic Asian	2	0.9
Unknown	2	0.9
Delivery method		
Vaginal	191	88.8
Cesarean section	17	7.9
Unknown	7	3.3
Firstborn child		
Yes	138	64.2
No	69	32.1
Unknown	8	3.7
Birth weight, pounds	201	7.1 (6.3, 7.8)
Term		
Preterm (<37 wk)	38	17.7
Early term (37 to <39 wk)	50	23.3
Full term (39 to <41 wk)	84	39.1
Late term (41 to <42 wk) or post-term (≥ 42 wk)	16	7.4
Unknown	27	12.6
Birth mothers (N = 190)		
Maternal age at delivery, y	187	22 (19, 27)
Mother born in the United States		
Yes	169	90.0
No	21	11.1
Maternal history of HPV vaccination relative to delivery		

Characteristic	n	% or median (IQR)
Not age-eligible ^a for HPV vaccination before delivery	73	38.4
Age-eligible ^a for HPV vaccination before delivery ^b	114	60.0
No	83	72.8
Yes, vaccinated after delivery	9	7.9
Yes, vaccinated with unknown timing	6	5.3
Yes, vaccinated before delivery	1	0.9
Unknown or invalid ^c vaccination date	15	13.2
Unknown HPV vaccination history	3	1.6
Maternal history of cervical cancer screening		
Yes	110	57.9
No	49	25.8
Unknown	31	16.3
Maternal history of anogenital warts		
Yes ^d	36	19.0
At time of delivery	24	66.7
Not at time of delivery	8	22.2
Unknown status at delivery	4	11.1
No	147	77.4
Unknown history of anogenital warts	8	4.2

Abbreviations: HPV, human papillomavirus; IQR, interquartile range; JORRP, juvenile-onset recurrent respiratory papillomatosis.

^aMother was age 26 y or younger in 2006 and child with JORRP was delivered in 2006 or later.

^bDenominator is total age-eligible for HPV vaccination.

^cReported date of HPV vaccination was before 2006.

^dDenominator is total with history of anogenital warts.

Table 2.

Clinical Characteristics of Children with Juvenile-Onset Recurrent Respiratory Papillomatosis (JORRP)—United States, 2015–2020

Characteristic	n	% or median (IQR)
Children with JORRP (N = 215)		
Presenting symptom/s ^a		
Hoarseness	204	94.9
Voice change	153	71.2
Difficulty breathing	63	29.3
Stridor	57	26.5
Abnormal cry	51	23.7
Difficulty swallowing	18	8.4
Other	12	5.6
Anatomic site/s ^a with papilloma		
Upper respiratory tract	13	6.1
Larynx	201	93.5
Lower respiratory tract	24	11.2
Number of anatomical sites ^b with papilloma at any time		
1	167	77.7
2	38	17.7
3	5	2.3
4	2	0.9
Unknown	3	1.4
Medical comorbidity ^a		
Asthma	26	12.1
Gastroesophageal reflux disease	21	9.8
Allergic rhinitis	14	6.5
Developmental delay	10	4.7
Obesity	5	2.3
Anxiety disorder	3	1.4
Down syndrome (trisomy 21)	3	1.4
Other ^c	17	7.9
Number of surgeries		
Lifetime	208	6 (3, 16)
Past 12 mo	215	2 (1,3)
Tracheostomy		
Yes, current or prior	9	4.2
No	199	92.6

Characteristic	n	% or median (IQR)
Unknown	7	3.3
History and type/s ^a of adjuvant therapy received		
None	51	23.7
Yes ^d	67	31.2
Cidofovir	47	70.2
Bevacizumab	13	19.4
Interferon	6	9.0
Indole-3-Carbinol	3	4.5
Artemisinin	2	3.0
Carboplatin	1	1.5
Other	15	22.4
Unknown	97	31.2

Abbreviations: IQR, interquartile range; JORRP, juvenile-onset recurrent respiratory papillomatosis.

^aNot mutually exclusive.

^bAnatomical sites: nose, oral cavity, pharynx, larynx, trachea, bronchus, tracheotomy site, pulmonary parenchyma, and other.

^cOther medical comorbidities: cerebral palsy, autism, obstructive sleep apnea, eczema, and other.

^dDenominator is total with history of adjuvant therapy.

Severity of Disease among Children with Juvenile-Onset Recurrent Respiratory Papillomatosis (JORRP), by Human Papillomavirus (HPV) Type—United States, 2015–2020

Table 3.

Characteristic	HPV Type				P-value
	n	% or median (IQR)	n	% or median (IQR)	
Severe disease ^b	58	44.3	19	76.0	<.01
Papillomas in the lower respiratory tract	11	8.4	6	24.0	.03
Number of surgeries, lifetime	128	6 (3, 13)	23	12 (4, 38)	.03
Number of surgeries, past 12 mo	131	2 (1, 3)	25	3 (2, 5)	<.01
Age at diagnosis, y	127	4.7 (2.7, 7.1)	22	2.2 (1.5, 3.5)	<.01

Abbreviations: IQR, interquartile range.

^aIncludes 1 child with HPV 6 and 44, and 1 child with HPV 6 and 54.

^bSevere disease is defined as one or more of the following: 10 lifetime surgeries, 4 surgeries in the past 12 mo, or papillomas in the lower respiratory tract.

Severity of Disease among Children with Juvenile-Onset Recurrent Respiratory Papillomatosis (JORRP), by Age at Diagnosis—United States, 2015–2020

Table 4.

Characteristic	Age at Diagnosis of JORRP				P-value
	n	% or median (IQR)	n	% or median (IQR)	
Severe disease ^a	68	70.1	34	30.9	<.01
Papillomas in the lower respiratory tract	17	17.5	7	6.4	.01
Number of surgeries, lifetime	92	13 (6, 26)	109	4 (2, 8)	<.01
Number of surgeries, past 12 mo	97	2 (1, 4)	110	2 (1, 3)	<.01
HPV type ^b	N = 72		N = 82		
HPV 6	53	73.6	74	90.2	<.01
HPV 11	18	25.0	4	4.9	<.01

Abbreviations: HPV, human papillomavirus; IQR, interquartile range; JORRP, juvenile-onset recurrent respiratory papillomatosis.

^aSevere disease is defined as one or more of the following: 10 lifetime surgeries, 4 surgeries in the past 12 mo, or papillomas in the lower respiratory tract.

^bTotal with specimens sufficient for HPV DNA typing; HPV not detected in all specimens.