

Initial Results From the National Registry for Juvenile-Onset Recurrent Respiratory Papillomatosis

Lori R. Armstrong, PhD; Craig S. Derkay, MD; William C. Reeves, MD; and the RRP Task Force

Objective: To characterize the spectrum of juvenile-onset recurrent respiratory papillomatosis (RRP) in the United States and to obtain data about the natural course of the disease and its response to treatment.

Setting: Twenty tertiary-care pediatric otolaryngology centers throughout the United States.

Patients: All patients with active RRP aged less than 18 years at the participating sites.

Main Outcome Measures: Number of surgical procedures performed per year, progression of papillomas to previously nondiseased anatomical sites, drug interventions and other adjuvant therapy, and need for tracheostomy.

Results: Data were collected from 399 children enrolled from January 1, 1997, through December 31, 1998. There were 51.9% male; 62.7% white, 28.3% black, 9.0% other or unknown racial group; 10.8% Hispanic ethnicity. Mean age at diagnosis was 3.8 years (range, 0.1-16.3

years) and mean duration of disease was 4.4 years (range, 0.03-18.9 years). The mean number of surgical procedures per child was 4.4 per year (range, 0.2-19.3 per year). Children whose RRP was diagnosed at younger ages (<3.0 years) were 3.6 times more likely to have more than 4 surgical procedures per year ($P = .001$) and almost 2 times more likely to have 2 or more anatomical sites affected ($P = .008$) than were children whose RRP was diagnosed at later ages (≥ 3.0 years), after adjusting for sex, race, and years of treatment.

Conclusions: Children whose disease was diagnosed before age 3 years were more likely than children aged 3 years or older to have more severe disease as measured by the mean number of surgical procedures performed and by the number of anatomical sites affected. The registry will form the basis for future analysis on the outcome of disease, natural course of RRP under management strategies, prevention strategies, and public health importance.

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From the Viral Exanthems and Herpesvirus Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Disease, Centers for Disease Control and Prevention, Atlanta, Ga (Drs Armstrong and Reeves); and Department of Otolaryngology, Head and Neck Surgery, Eastern Virginia Medical School, Norfolk (Dr Derkay). A list of the principal investigators of the RRP Task Force appears on page 744. Dr Armstrong is now with the Division of Cancer Prevention and Control, Cancer Surveillance Branch, Centers for Disease Control and Prevention.

RECURRENT respiratory papillomatosis (RRP) is a chronic disease caused by human papillomavirus types 6 and 11. The most common site of lesions is the larynx, but papillomas can occur throughout the respiratory and upper gastrointestinal tracts. Juvenile-onset RRP (JORRP) presumably occurs by transmission of human papillomavirus from infected mothers to their infants, but the exact mechanism of transmission is unknown.¹ Frequent recurrence of disease, despite surgical extirpation, results in airway compromise, permanent and transient voice changes, and substantial childhood morbidity. Surgical removal of laryngeal papillomas is often necessary every 1 to 2 months, placing extreme financial and psychological hardships on the patients and their families. Death occurs in RRP when papillomas obstruct the airway or spread to the lung parenchyma.² Medical

treatments, such as interferon alfa, acyclovir, retinoids, and indole-3-carbinol, have been used to treat RRP, with mixed success.³

Still unknown are the incidence and prevalence of RRP, the various aspects of the clinical course, the most effective methods of treatment, and the mechanisms of human papillomavirus transmission. In 1994, a survey of members of the American Academy of Otolaryngology-Head and Neck Surgery, the American Society of Pediatric Otolaryngology, and the American Bronchoesophagological Association showed that more children had severe RRP, defined as requiring more than 10 operations in their lifetime, than previously thought. Thirty-

This article is also available on our Web site: www.ama-assn.org/oto.

PATIENTS AND METHODS

In January 1997, the Centers for Disease Control and Prevention started a national JORRP registry involving 20 study sites at tertiary-care medical centers around the United States. Sites were chosen among institutions affiliated with members of the American Society of Pediatric Otolaryngology on a voluntary basis, but with an attempt to choose medical centers dispersed throughout the United States that had large numbers of pediatric patients with RRP. To standardize data collection, site coordinators attended a 1-day instructional seminar to learn how to identify patients for the registry and to use the study's medical record abstraction form. A 2-page medical record abstraction form was used to collect basic demographic data, information about the progression of illness, anatomical sites affected, pertinent medications, surgical and other interventions, and insurance coverage on all children younger than 18 years with RRP who were treated at each site from January 1, 1996, 1 year before the registry, through December 31, 1998. During this period, site coordinators collected information about all patients with RRP from the time they were first seen at the site until the end of the registry period, or until the patient became unavailable for follow-up, was transferred to a nonregistry site, or died. If available, retrospective data for all patients were collected back to the time of diagnosis, even if their diagnosis occurred at a location other than the registry site.

Site coordinators identified patients by checking current and past operating room (OR) records and, if possible, computer records of billing codes for microlaryngoscopy with removal of tumor (billing code 31541), or the *International Classification of Diseases, Ninth Revision*, code for benign neoplasm of the larynx (212.1). Statistical analyses, such as logistic regression and Mantel-Haenszel χ^2 for categorical data, and the Kruskal-Wallis test and Wilcoxon 2-sample test for continuous data not normally distributed, were performed by means of SAS statistical software (SAS Institute Inc, Cary, NC).

This project and complete study protocols were approved by the Centers for Disease Control and Prevention Human Subjects Review Committee (protocol 1519).

three percent of children studied required more than 20 operations in their lifetime, with 7% of these requiring more than 100 surgical procedures.⁴ To learn more about JORRP, the Centers for Disease Control and Prevention, in collaboration with members of the American Society of Pediatric Otolaryngology, established a national registry of children with JORRP in 1997.

The registry, which is scheduled to continue until December 31, 1999, provides the first opportunity to learn about JORRP on a national level and, to our knowledge, is the only surveillance system for the disease. The registry will form the basis for establishing the public health importance of JORRP and developing prevention strategies. The overall objectives of the RRP registry are to improve

Principal Investigators of the RRP Task Force

Long Island Jewish Medical Center, New Hyde Park, NY: Allan Abramson, MD. Rainbow Babies and Children's Hospital, Cleveland, Ohio: James Arnold, MD. University of Iowa Hospitals and Clinics, Iowa City: Nancy M. Bauman, MD, Richard J. H. Smith, MD. University of Alabama, Birmingham: Thomas R. Broker, PhD. University of Texas Southwestern Medical Center, Dallas: Orval E. Brown, MD, John E. McClay, MD. Children's National Medical Center, Washington, DC: Sukgi S. Choi, MD, Scott R. Schoem, MD, George H. Zalzal, MD. University of Utah, Salt Lake City: Steven D. Gray, MD, Steven M. Kelly, MD. Children's Hospital of Philadelphia, Philadelphia, Pa: Steven D. Handler, MD, Ian Jacobs, MD, William P. Potsic, MD, Lawrence W. C. Tom, MD, Ralph F. Wetmore, MD. Children's Hospital and Medical Center, Seattle, Wash: Andrew F. Inglis, Jr, MD, Scott C. Manning, MD. The Johns Hopkins Medical Institutions, Baltimore, Md: Haskins Kashima, MD, Anthony E. Magit, MD, David E. Tunkel, MD. Children's Hospital and Health Center, San Diego, Calif: Donald B. Kearns, MD, Seth M. Pransky, MD. University of California, Irvine: Carol MacArthur, MD, Ayal Willner, MD, Nina S. Yoshpe, MD. Nemours Children's Clinic, Jacksonville, Fla: Bruce R. Maddern, MD. St Louis Children's Hospital, St Louis, Mo: Harlan R. Muntz, MD. Children's Hospital Medical Center, Cincinnati, Ohio: Charles M. Myer III, MD. University of Tennessee, Memphis: Rosemary Stocks, MD, Jerome W. Thompson, MD. The Emory Clinic, Atlanta, Ga: N. Wendell Todd, MD. Vanderbilt Medical School, Nashville, Tenn: Jay A. Werkhaven, MD, and Children's Hospital of Alabama, Birmingham: Brian J. Wiatrak, MD.

existing knowledge about RRP by characterizing the level of disease in the United States and to improve prognosis by providing a greater understanding of the natural course of the disease and its response to treatments. The specific aims of the registry are to (1) establish a cohort of patients with RRP that will be followed for 3 years; (2) determine the extent and severity of disease (eg, results of biopsy, length of time between recurrences of laryngeal papillomas, number of treatments per child, and outcome of treatments); and (3) determine the most commonly used types of surgical and pharmacological treatment.

We present the initial results from the first 2 years of the national surveillance system for JORRP. Demographics of children registered, the clinical features, and factors associated with severe disease are presented.

RESULTS

As of December 31, 1998, 399 children were enrolled in the registry from 20 registry sites (**Table 1**). The average age at initial registration was 7.9 years (range, 0.3-20.9 years). Boys slightly ($n = 207$ [51.9%]) outnumbered girls ($n = 192$ [48.1%]). Sixty-three percent ($n = 250$ [62.7%]) of children were white, 28.3% ($n = 113$) were black, 2.3% ($n = 9$) were Asian-Pacific Islander or American Indian-Alaskan Native, and 3.3% ($n = 13$) were listed as biracial or other race. Race was unknown for 3.5% ($n = 14$) of the children. (Because of

Table 1. RRP Registry Participants and Numbers of Children Registered, December 31, 1998*

Registry Site	No. of Children Registered
Children's Hospital of Alabama, Birmingham	32
Children's Hospital and Health Center, San Diego, Calif	25
University of California, Irvine	13
Children's National Medical Center, Washington, DC	21
Nemours Children's Clinic, Jacksonville, Fla	18
Egleston Hospital/Emory Clinic, Emory University, Atlanta, Ga	18
University of Iowa Hospital and Clinics, Iowa City	19
The Children's Hospital, Boston, Mass	15
Johns Hopkins Medical Institute, Baltimore, Md	13
St Louis Children's Hospital, St Louis, Mo	18
Long Island Jewish Medical Center, New Hyde Park, NY	19
Cincinnati Children's Hospital, Cincinnati, Ohio	23
Rainbow Babies and Children's Hospital, Cleveland, Ohio	21
Children's Hospital of Philadelphia, Philadelphia, Pa	26
University of Tennessee, Memphis	6
Vanderbilt University, Nashville, Tenn	24
University of Texas Southwestern Medical Center, Dallas	38
University of Utah, Salt Lake City	4
Eastern Virginia Medical School, Children's Hospital of the King's Daughters, Norfolk	19
Children's Hospital and Medical Center, Seattle, Wash	27
Total	399

*RRP indicates recurrent respiratory papillomatosis.

rounding, percentages for race do not total 100). Only 52.9% of all children had ethnicity data available; 10.8% (n = 43) were reported as Hispanic. The average age at diagnosis was 3.8 years and mean duration of disease was 4.4 years (**Table 2**). However, a peak in the average age at diagnosis appeared at year 2 (**Figure**), reflecting the median age at diagnosis of 2.8 years. The age at diagnosis and years of disease did not differ significantly between boys and girls (Table 2).

Overall, 8082 procedures were reported; 91.1% (n = 7365) were performed in the OR, 8.1% (n = 656) were performed in the clinic, and location was not specified for 0.8% (n = 61) of procedures. The average number of all recorded procedures per child was 20.3 (median, 12 procedures; range, 1-151). Typically, procedures performed in the OR were for papilloma removal, and procedures performed in the clinic were for diagnosis. Because OR procedures accounted for most procedures, counting only OR (mean, 18.6 per child) or both clinic and OR procedures (mean, 20.3 per child) showed little difference in the number of lifetime procedures. There was no difference in the average number of lifetime procedures (clinic and OR) between boys (mean, 20.7; median, 13; range, 1-151) and girls (mean, 19.8; median, 11.5; range, 1-114).

Forty-two children (11%) had tracheostomies recorded, and 15 (36%) of those were decannulated. The mean age at tracheostomy was 2.7 years for the 31 children for whom age at tracheostomy was known (range, 0.5-7.9 years). The mean age at diagnosis for children who underwent tracheostomy (n = 35) was 2.7 years (range, 0.3-14.8 years), which was significantly lower than the mean age at diagnosis for children who had never had a tracheostomy (n = 308; mean, 3.9 years; range, 0.1-

Table 2. Clinical Characteristics by Sex of Child

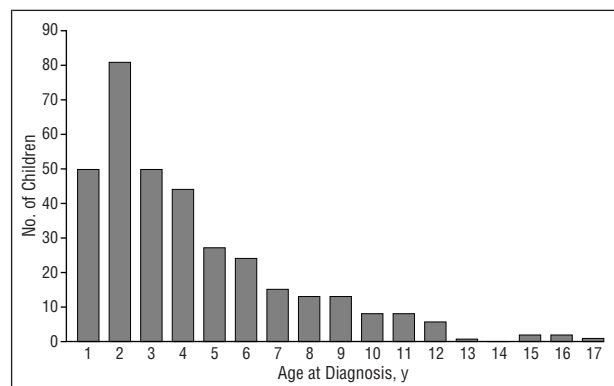
	No.	Mean	Median	Range	P*
Age at diagnosis†					
Boys	184	3.5	2.7	0.1-16.3	.32
Girls	164	4.0	3.1	0.17-15.8	
Total	348	3.8	2.8	0.1-16.3	
Years with disease‡					
Boys	184	4.2	3.3	0.03-18.9	.88
Girls	164	4.5	2.8	0.1-16.5	
Total	348	4.4	3.0	0.03-18.9	
No. of procedures per year (performed in clinic and OR)†§					
Boys	184	5.1	4.2	0.2-19.8	.24
Girls	164	4.6	3.9	0.5-14.5	
Total	348	4.9	4.0	0.2-19.8	
No. of surgical procedures per year (performed in OR only)†§					
Boys	184	4.6	3.9	0.2-19.3	.26
Girls	162	4.2	3.7	0.3-13.2	
Total	346	4.4	3.8	0.2-19.3	

*Wilcoxon rank-sum test.

†Age at diagnosis, years with disease, and number of surgical procedures per year were based on the date of diagnosis. Fifty-one children were missing the date of diagnosis and were removed from this analysis.

‡Age at last recorded procedure - age at diagnosis.

§Number of procedures (clinic and operating room [OR]) and the number of surgical procedures (OR only) per year equals average number of procedures performed per year. For children with disease duration < 1 year, the mean number of procedures per year equals the number of procedures during the first year. For number of surgical procedures (OR only), n = 346 children; date of diagnosis was missing for 51 children and no OR procedures were recorded for 2 additional children.



Distribution of age at diagnosis for children enrolled in the recurrent respiratory papillomatosis registry.

16.3 years; Wilcoxon rank-sum test, $P = .001$) and for whom age at diagnosis was known.

The mean number of procedures per year (counting both OR and clinic-based procedures) was 4.9 (range, 0.2-19.8 procedures per year) for children whose age at diagnosis was known (n = 348) (Table 2). For this analysis, the mean number of procedures was calculated by dividing the number of lifetime procedures by the years of disease in children who had had RRP for 1 year or more. For children who had had RRP for less than 1 year, the mean number of procedures was counted as their total number of OR and clinic procedures. Sixty-four children (16%) in the registry had had RRP for less than 1 year. The mean number of procedures was calculated according to sex for both procedures

Table 3. Clinical Characteristics by Race and Ethnicity of Child

	No.	Mean	Median	Range	P*
Age at diagnosis†					
White	218	3.6	2.6	0.1-15.7	.55
Black	98	3.8	3.0	0.01-11.8	
Other	19	4.0	2.3	0.6-14.1	
Hispanic	42	3.7	3.5	0.7-11.3	.99
Non-Hispanic	141	4.0	3.2	0.01-15.7	
Years with disease†‡					
White	218	4.7	3.4	0.01-18.9	.09
Black	98	3.7	2.5	0.01-16.5	
Other	19	4.4	4.6	0.02-12.4	
Hispanic	42	5.3	4.1	0.02-15.9	.27
Non-Hispanic	141	4.5	2.9	0.01-17.4	
No. of surgical procedures per year (OR only)†§					
White	216	4.6	4.0	0.3-19.3	.05
Black	98	3.8	3.2	0.2-12.9	
Other	19	5.2	4.6	0.9-13.3	
Hispanic	42	5.0	4.2	0.7-13.5	.13
Non-Hispanic	141	4.1	3.3	0.2-13.3	

*Kruskal-Wallis test was used for comparison of racial groups. Wilcoxon rank-sum test was used for comparison of ethnic groups.

†Age at diagnosis, years with disease, and number of surgical procedures per year were based on the date of diagnosis. The date of diagnosis was missing for 51 children, and their data were removed from this analysis. Children who had missing or unknown race (n = 14) and ethnicity (n = 216) or unknown date of diagnosis (additional 50 children) were removed from analysis.

‡Age at last recorded procedure – age at diagnosis.

§Average number of surgical procedures performed in the operating room (OR) per year.

Table 4. Demographic and Clinical Features as Risk Factors for More Than 4 Mean Surgical Procedures per Year for 336 Registered Children*

Feature	Unadjusted Odds Ratio	P	Adjusted Odds Ratio	P
Age at diagnosis <3.0 y	3.3	<.001	3.6	<.001
Sex				
Male	Reference	NA	Reference	NA
Female	0.87	.53	0.9	.52
Race				
White	Reference	NA	Reference	NA
Black	1.5	.12	1.4	.19
Other†	0.76	.57	0.8	.73

*Number of children for whom all data were available (age at diagnosis, sex, race). Logistic regression Hosmer-Lemeshow goodness-of-fit test statistic, 3.3; P = .86. Number of surgical procedures equals average number of surgical procedures performed in the operating room per year. NA indicates not applicable.

†Designates 22 children recorded as Asian, Pacific Islander, American Indian, Alaska Native, and other race, including biracial children.

performed in the OR and clinic and for procedures in the OR only (surgical procedure). Although the mean number of procedures decreased to 4.4 per year when only surgical procedures were calculated, these differences did not differ statistically. No significant differences were noted for the average number of procedures (clinic and OR) between boys and girls (Table 2). Further discussion of the mean number of procedures per year will refer to procedures performed in the OR only (surgical procedures). Racial and ethnic

Table 5. Mean Number of Surgical Procedures per Year Grouped by Age at Diagnosis

Age at Diagnosis, y	No. of Children	Year of Disease	No. of Surgical Procedures, Mean (Range)
0-2	114	1st	6.8 (1-27)
	99	2nd	6.4 (1-25)
	82	3rd	5.9 (1-33)
	61	4th	5.6 (1-27)
	53	5th	5.1 (1-23)
>2-5	107	1st	4.8 (1-14)
	89	2nd	5.2 (1-29)
	83	3rd	4.5 (1-22)
	56	4th	4.0 (1-18)
	44	5th	3.9 (1-19)
>5-8	45	1st	4.0 (1-11)
	33	2nd	3.8 (1-14)
	27	3rd	3.0 (1-13)
	19	4th	3.7 (1-14)
	12	5th	4.1 (1-16)
>8	37	1st	2.9 (1-10)
	23	2nd	3.0 (1-11)
	14	3rd	2.6 (1-7)

groups did not differ in these clinical features except for mean number of surgical procedures per year (Table 3). Blacks had the fewest surgical procedures per year (mean, 3.8), and whites followed with a mean of 4.6 surgical procedures per year. Children listed in other racial groups (nonwhite, non-black) had the greatest mean number of surgical procedures per year, with 5.2 (Kruskal-Wallis test, P = .05). Hispanics also differed in their mean number of surgical procedures per year, with 5.0, compared with non-Hispanics at 4.1 per year, but the difference was not statistically significant (Wilcoxon rank-sum test, P = .13; Table 3).

Children whose RRP had been diagnosed before 3 years of age had a higher mean number of surgical procedures per year. Table 4 shows the results of multivariate analysis (logistic regression) comparing age at diagnosis, sex, and race with the lifetime mean number of surgical procedures. Children whose RRP had been diagnosed before 3 years of age were 3.6 times more likely to have a lifetime mean of more than 4 surgical procedures per year after adjusting for sex and race. Factors such as sex and race were not associated with lifetime mean surgical procedures of more than 4 per year. Hispanic ethnicity was not used in the logistic regression model because this information was available for only 52.9% of the children in the registry. The observation that children whose RRP was diagnosed at younger ages were more likely to accrue a higher mean number of surgical procedures per year appears again in Table 5. Children whose RRP was diagnosed before age 2 years had more mean surgical procedures per year (5.1-6.8) for the first 5 years of disease than did children whose RRP was diagnosed at older ages. Their mean number of surgical procedures per year decreased steadily for each year after diagnosis from 6.8 in the first year to 5.1 in the fifth year. In general, these means are higher than comparable years of disease for children diagnosed after age 2 years.

The majority of children (n = 382 [95.7%]) had laryngeal involvement (Table 6). Seventeen children who had no laryngeal involvement had papilloma lesions re-

Table 6. Papilloma Involvement at Anatomical Sites for 399 Children Enrolled in the RRP Registry*

Anatomical Site	No. (%)
Larynx	382 (96)
Trachea	123 (31)
Oropharynx or nasopharynx	82 (21)
Hypopharynx	43 (11)
Bronchus	23 (6)
Esophagus	8 (2)
Pulmonary	3 (1)

*Children were counted once for each anatomical site affected during their lifetime. The percentages for each anatomical site represent the fraction of 399 children affected at that site. RRP indicates recurrent respiratory papillomatosis.

ported in the oropharynx, nasopharynx, mouth, trachea, or lung. Forty-eight percent of children ($n = 193$ [48.4%]) had sites involved outside the larynx and 31.3% ($n = 125$) outside both the larynx and trachea. All children with bronchial (5.8% [$n = 23$]) or pulmonary (0.8% [$n = 3$]) involvement had tracheal involvement as well. Eight children (2.0%) had esophageal involvement. More than half of the children ($n = 210$ [52.6%]) had only 1 site affected, 24.6% ($n = 98$) of children had 2 sites affected, 9.5% ($n = 38$) had 3 sites affected, and 11.5% ($n = 46$) of children had 4 or more sites affected (data not shown). **Table 7** and **Table 8** compare children according to total number of affected sites throughout their childhood and age at diagnosis. The mean age at diagnosis was 4.3 years for children with only 1 site affected but dropped to 3.2 years when 2 or more sites were affected (Table 7). The multivariate analysis (Table 8) showed that RRP in children diagnosed before 3.0 years of age was 1.8 times more likely to result in papilloma at 2 or more anatomical sites than it was in children diagnosed at age 3.0 years or later. The years of treatment were also positively associated as a risk factor for the number of anatomical sites affected. The years of treatment were determined as the time between the date of the first recorded surgery and the date of the last recorded surgery. This factor was added to the model to account for children who had not been followed consistently since diagnosis and might thus be missing recorded procedures. Factors not associated with 2 or more anatomical sites affected were sex and race of the child.

COMMENT

This report describes the initial results from the first 2 years of a 3-year national registry for JORRP. Data from 399 children who were treated at tertiary otolaryngology centers were described from their onset of disease to their current status. This study describes children with RRP based on data from a national surveillance system, describes differences in racial groups among children with RRP, and provides statistical validation of previously observed findings on the severity of disease on a national level.

Data collected for the registry were used to determine measurements of the severity of disease. Certain clinical features, such as an early age at diagnosis, were associated with a higher mean number of surgical pro-

Table 7. Number of Sites Affected and Mean Age at Diagnosis

No. of Sites Involved	No.*	Age at Diagnosis		
		Mean	Median	Range
1	191	4.3	3.3	0.1-16.3
≥2	153	3.2	2.3	0.1-15.6
≥3	66	2.8	1.8	0.1-15.6

*Number for which age at diagnosis was known. Fifty-one children had unknown age at diagnosis.

Table 8. Demographic and Clinical Features as Risk Factors for 2 or More Anatomical Sites Affected for 336 Registered Children*

Feature	Unadjusted Odds Ratio	P	Adjusted Odds Ratio	P
Age at diagnosis <3.0 y	1.9	.005	1.8	.008
Years of treated disease	1.2	<.001	1.2	<.001
Sex				
Male	Reference	NA	Reference	NA
Female	0.9	.40	0.8	.35
Race				
White	Reference	NA	Reference	NA
Black	0.9	.60	1.1	.80
Other	1.1	.90	1.1	.90

*Number of children for whom all data were available (sites affected, age at diagnosis, years of treatment, sex, race). Logistic regression Hosmer-Lemeshow goodness-of-fit test statistic, 3.3; $P = .91$. NA indicates not applicable.

cedures per year required over a lifetime and with a greater number of anatomical sites affected with papilloma. Race was associated with a high mean number of surgical procedures per year in the univariate analysis, but not in the multivariate analysis. The univariate association between race and high number of surgical procedures per year may result from the high mean number of procedures in children listed as "other" race (mean number of surgical procedures, 5.2 per year). Because of the small number of children in this group, race as "other" did not hold up as a risk factor for high mean number of surgical procedures per year in the multivariate analysis. Ethnic group as a risk factor for a high mean number of surgical procedures per year was not measured in the logistic regression model because of lack of data. The association between a high mean number of surgical procedures (>4) per year and younger age at diagnosis (<3 years) may be caused by anatomical differences during their early years rather than the severity of disease. Younger children, with smaller airways, have a greater likelihood of airway occlusion from papillomas than older children. Therefore, clinicians may be inclined to schedule operative endoscopies in younger children with RRP before symptoms develop to avoid potential airway compromise. The other measurement used for severity of illness in this study, the number of anatomical sites affected, may better reflect actual severity of disease. Considering the possibility that the risk of reactivation at an anatomical site increases with the excision of papilloma,⁵ it is likely that these 2 factors, mean number of

surgical procedures per year and number of anatomical sites affected, are related.

These findings are consistent with those of other studies regarding certain clinical aspects of JORRP. Case series studies conducted in Sweden⁶ and Australia⁷ have found the mean age at diagnosis (3.7 and 4.9 years, respectively) to be within 1.1 years of the mean of 3.8 years described herein and reported similar wide ranges in the age at diagnosis (0.5-16 years and 0.5-21 years, respectively). A similar sex distribution (male-female ratio, 11:10) has been reported previously.⁶ Children in the registry who were recorded as ever having had a tracheostomy also had a younger mean age at diagnosis of RRP (2.7 years) than children who had never had a tracheostomy (3.9 years). A younger age at diagnosis was associated with more severe RRP in our study. Children enrolled in the registry were mainly from tertiary care medical centers and may represent a population with more severe RRP or with secondary medical conditions that require tracheostomy.

The distribution of anatomical sites affected corresponds to that in other reports. Pulmonary spread remains a rare event, occurring in only 0.8% of all children in our study, and this finding agrees with what others have reported.^{2,8} Involvement outside the larynx was seen in 48.4% of children, which is significantly greater than the 31% documented in a nationwide survey of otolaryngologists reporting on children with RRP.⁴ In 30.8% of children in the registry, papillomas had spread to the trachea, which is a greater percentage than previously reported. Kramer et al,⁸ in a review of the literature, reported that only 5% of children had involvement of the trachea and/or proximal bronchi and 9% had tracheal involvement in a Danish study.⁹ The increased involvement outside the larynx in children described herein may reflect a population of patients with more severe disease who have been referred to the tertiary care medical centers that are participants in the registry.

The registry is the first national surveillance system for this rare disease. Collection of surveillance data in the form of a registry was successfully implemented at 20 study sites. The information collected was chosen to ensure a high standard quality of data and easy accessibility and recording for site coordinators. More extensive data collection systems, such as recording the specific anatomical sites affected and medical history, can give more information about the clinical features of each child. However, if detailed information is to be accurately collected for a national registry, the information must be recorded in a standard fashion into the medical record by all otolaryngologists caring for children with RRP.

The registry of 399 US children with RRP has yielded further insights into the clinical course of the disease. This initial report documented that an early age at diagnosis, the years of treatment for RRP, the number of anatomical sites affected, and the number of lifetime surgical procedures were associated with more severe disease. Future analyses of the registry data will provide information on the disease outcome, survival analysis, pharmacological treatment, histological characteristics of papilloma associated with disease severity and outcome, and the effects of tracheostomy. The national registry is a unique surveillance system that will provide information about the regional differences in disease characteristics. The registry will also pro-

vide information about the trends of disease treatment and changes in the trends of disease onset and severity and form the basis for prevention strategies and studies of the public health importance of JORRP.

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The use of trade names and commercial sources is for identification purposes only and does not constitute endorsement by the Public Health Service of the US Department of Health and Human Services.

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Corresponding author: Lori R. Armstrong, PhD, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Cancer Prevention and Control, Cancer Surveillance Branch, Mail Stop K-53, 4770 Buford Hwy NE, Atlanta, GA 30341 (e-mail: lra0@cdc.gov).

Reprints: Viral Exanthems and Herpesvirus Branch, Centers for Disease Control and Prevention, Mail Stop A-15, 1600 Clifton Rd NE, Atlanta, GA 30333.

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