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Recurrent respiratory papillomatosis: Recent advances in HPV-6/HPV-11–targeted immunotherapy

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Abstract

Recurrent respiratory papillomatosis (RRP) is caused by human papillomavirus (HPV) types 6 and 11. Juvenile-onset RRP (JoRRP), typically acquired during birth, and adult-onset RRP (AoRRP), commonly associated with sexual transmission, are both predominantly caused by HPV-6, followed by HPV-11. HPV-11 infection, more frequent in children, is associated with more severe disease, increased risk of tracheobronchial and pulmonary spread, and, rarely, RRP-related mortality. Local immune tolerance within the airway mucosa is thought to impair clearance of HPV-6/11–infected cells, resulting in persistent infection and recurrent papilloma growth. Surgical debulking remains the cornerstone of management; however, JoRRP requires substantially more procedures than AoRRP (4–8 vs 1–2 per year), leading to cumulative morbidity, including vocal fold scarring, anterior commissure webbing, glottic or subglottic stenosis, and pulmonary dissemination.

Defective innate immune activation and impaired HPV-specific cellular immunity contribute to viral persistence, with the papilloma microenvironment characterized by ineffective antiviral T-cell responses. To reduce surgical burden, immunotherapeutic strategies targeting HPV-6/11 antigens have been developed. Three platforms have advanced into phase 1–2 clinical trials: a gorilla adenoviral vector (gAdeno)–based therapy, a DNA plasmid vaccine, both encoding HPV-6/HPV-11 E6/E7 oncoproteins, and a Modified Vaccinia Ankara (MVA)–based bovine papillomavirus E2 vaccine. These approaches aim to elicit robust E6/E7-specific cellular immunity, particularly $CD8^+$ T-cell responses, to overcome local immune tolerance and eradicate HPV-infected cells. The gAdeno-based therapy is the first FDA-approved immunotherapy for RRP; however, with annual treatment costs exceeding USD 300,000, ensuring equitable access remains a critical challenge.

Key words: Recurrent respiratory papillomatosis, HPV-6, HPV-11, Juvenile-onset recurrent respiratory papillomatosis (JoRRP), Adult-onset recurrent respiratory papillomatosis (AoRRP), Targeted immunotherapy

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Introduction

Recurrent respiratory papillomatosis (RRP) is characterized by the development of benign epithelial tumors, or papillomas, in the respiratory tract. These lesions predominantly affect the larynx but can also involve the pharynx, trachea, bronchi, and, in rare cases, pulmonary parenchyma. Despite their benign histological nature, these lesions can significantly impair health through airway obstruction, dysphonia, and necessitating repeated medical interventions. RRP is primarily associated with infections from low-risk human papillomavirus (HPV) types, notably HPV-6 and HPV-11. The prevalence of HPV-6 and HPV-11 in different RRP and non-RRP cohorts is summarized in **Figure 1**. This disease manifests in both children (juvenile-onset) and adults (adult-onset), with juvenile cases often presenting earlier, behaving more aggressively, and exhibiting higher rates of recurrence.

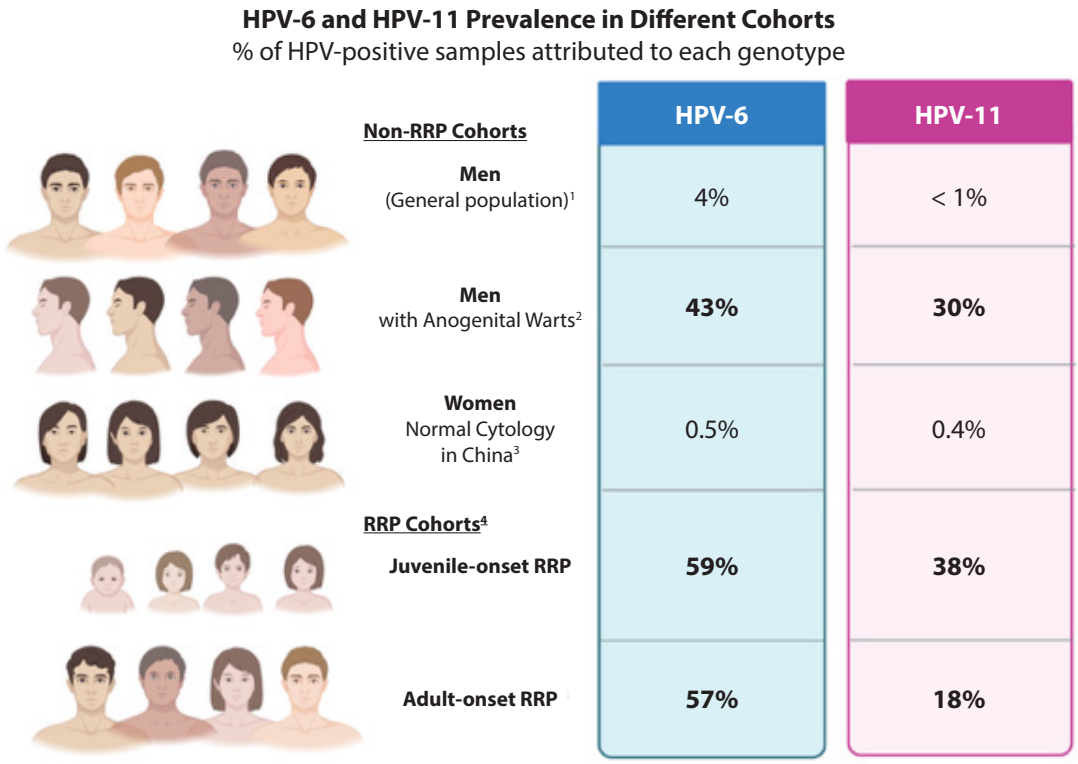

Figure 1A. Prevalence of Human Papillomavirus (HPV) Genotypes 6 and 11 across Different Clinical and Population Cohorts.

This review examines recent advances in the epidemiology, clinical aspects, immunopathogenesis, and clinical development of HPV-6/11–targeted immunotherapy, including the first-in-class approved adenoviral vector–based therapy.

Geogrpahic Incidence and Prevalence of RRP (Table 1 and Figure 1B-1C)

The overall incidence of RRP is estimated to be approximately **3.5 cases per 100,000 individuals** in the general population.[1] For juvenile-onset recurrent respiratory papillomatosis (JoRRP), estimated incidence ranges from approximately 0.2 to 2.1 per 100,000 children per year across various populations, with the peak age typically between 2 and 4 years.[2] In developed countries, the incidence tends to be lower, around 0.17 to 0.5 per 100,000 children per year. Ecological studies and national registry reports from countries such as Australia and several European nations indicate significant reductions in JoRRP incidence following high vaccine uptake, with some studies reporting declines of over 70% in new pediatric cases.

The incidence of adult-onset RRP (AoRRP) varies approximately 0.2 to 3.9 per 100,000 adults per year, with incidence peaks in both young and older adults.[2,3,4] Adult incidence trends are less well-defined, and the impact of vaccination on AoRRP may be delayed or limited by prior HPV exposure.

Geographical variation in incidence arises from differences in HPV prevalence, maternal genital warts prevalence, obstetric practices, healthcare access, and surveillance systems. Incidence can be underreported due to variable registry and reporting practices. Although the overall incidence is low, the disease burden per case is substantial due to frequent recurrences and repeated medical interventions. The median number of procedures per patient and lifetime healthcare utilization underscore the considerable morbidity associated with RRP, despite its low incidence.

Route of Transmission

1. **Juvenile-Onset RRP (JoRRP)**

   Transmission Route: JoRRP is primarily transmitted perinatally during childbirth. Infants can acquire HPV from an infected mother through the birth canal.[18,19]

   Risk Factors: Infected mothers, particularly those with genital warts or an active HPV infection at the time of delivery, have a higher risk of transmitting the virus to their infants.[18,19]

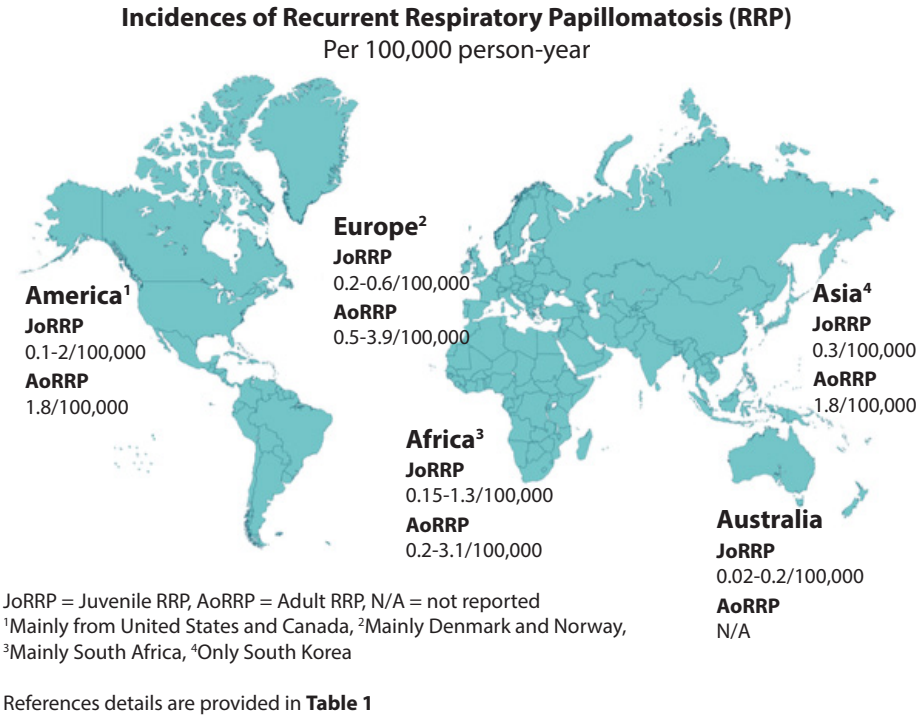

Figure 1B. Geographic Incidences of Recurrent Respiratory Papillomatosis (RRP) Per 100,000 person-year.

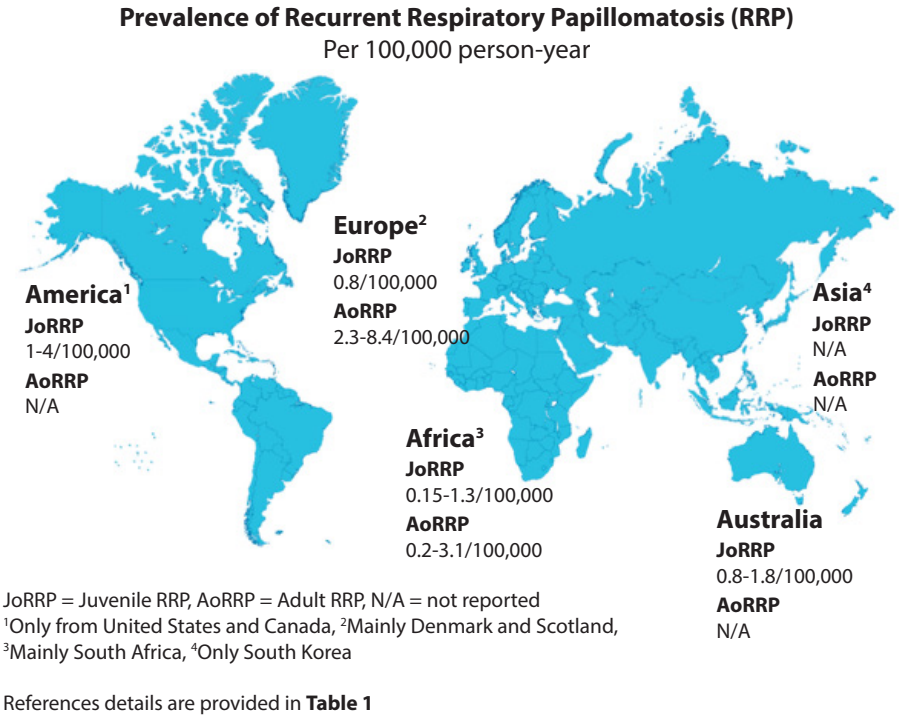

Figure 1C. Geographic Prevalence of Recurrent Respiratory Papillomatosis (RRP).

Table 1. Incidence of RRP stratified by regional area.

Study (Year)	Country	Year	Age (years)	Number of subjects (Population base study)	Incidence (per 100,000 person years)	Prevalence (per 100,000 person years)
America						
JoRRP						
- Derkay, 1995[5]	United States	1993	< 14	55,000,000	4.3	-
- Armstrong, 2000[6]	United States	1996	0-18	1,638,066	0.1-2.1	1.0-4.0
- Campisi, 2010[7]	Canada	1994-2007	0-14	NA	0.2	1.1
- Marsico, 2014[8]	United States	2006	0-17	3,635,064	0.5-1.0	1.5-2.9
- Meites, 2021[9]	United States	2004-2005	< 18	NA	2.9	-
		2012-2013	< 18		0.7	-
AoRRP						
- Derkay, 1995[5]	United States	1993-1994	> 18	200,000,000	1.8	-
Europe						
JoRRP						
- Bomholt, 1988	Denmark	1980-1983	0-14	300,000	0.6	0.8
- Lindeberg, 1990[10]	Denmark	1974-1993	0-20	2,800,000	3.6	-
- Omland, 2012[11]	Norway	1987-2009	0-17	2,600,000	0.2	-
AoRRP						
- Bomholt, 1988[12]	Denmark	1980-1983	> 18	1,440,000	0.8	2.3
- Lindeberg, 1990[10]	Denmark	1974-1993	> 20	2,800,000	3.9	-
- Omland, 2012[11]	Norway	1987-2009	> 18	1,100,000	0.5	-
- Blackwell, 2015[13]	Scotland	2003-2014	> 18	800,000	-	8.4
Australia						
JoRRP						
- Novakovic, 2018[14]	Australia	2010-2018	< 15	NA	0.02-0.1	0.8-1.8
- Zurynski, 2018[15]	Australia	2012	< 16	NA	0.2	-
		2016	< 16		0.02	-
Asia						
JoRRP						
- Oh, 2021[16]	Korea	2002-2014	0-12	NA	0.3	-
Africa						
JoRRP						
- Seedat, 2018[3]	Lesotho	2011-2013	0-14	NA	0.15	1.0
	South Africa	2011-2015	0-14	NA	1.3	3.9
AoRRP						
- Seedat, 2018[3]	South Africa	2011-2015	> 18	NA	0.2	0.4
- Ndour, 2020[17]	South Africa	2009-2018	> 18	NA	3.1	-

2. Adult-Onset RRP (AoRRP)

Transmission Route: AoRRP typically arises from sexual transmission through direct inoculation of human papillomavirus (HPV), particularly types 6 and 11, into the upper airway mucosa via oral-genital contact.[20,21] Alternatively, AoRRP may result from reactivation of a long-standing latent infection acquired earlier in life; however, this reactivation mechanism remains hypothetical and unproven at the population level. Current evidence supports the biological plausibility of HPV latency and reactivation within the airway mucosa but cannot yet quantify the relative contribution of reactivation versus de novo adult infection to AoRRP.[22,23]

Risk Factors: Behavioral factors, such as having multiple sexual partners or a history of sexually transmitted infections (20, 21), may increase the likelihood of HPV transmission and subsequent development of AoRRP.

Clinical Presentation

The clinical symptoms of recurrent respiratory papillomatosis depend on the anatomical site of involvement within the respiratory tract (24, 25), as well as the size, number, and growth rate of the lesions. The anatomical distribution of papillomatosis is summarized in **Figure 2A**.

The manifestations vary based on age-onset (**Table 2**), anatomic involvement and its extension :

1. **Laryngeal lesions (Figure 2B and 2C)**
   The most common presenting symptom is progressive hoarseness or dysphonia. Patients frequently report vocal fatigue and may exhibit a breathy or weak voice. In cases with large lesions, aphonia may occur. The severity of voice changes is closely related to the extent of glottic involvement and the bulk of the lesions.

2. **Pharyngeal lesions**
   This may manifest as a globus sensation, dysphagia, frequent throat clearing, and odynophagia, especially when lesions are extensive.

3. **Subglottis, Trachea, Bronchus and Lung parenchyma (Figure 2D)**
   Lesions in these areas often cause biphasic or inspiratory stridor, noisy breathing, exertional dyspnea, chronic cough, wheezing, recurrent pneumonias, chronic productive cough, and hemoptysis. Severe disease in these regions may result in significant airway obstruction.
   During a physical examination, papillomatous lesions can often be visibly identified in the affected areas through direct examination or endoscopy. Endoscopic evaluation is essential for accurately diagnosing and assessing the extent of the disease.

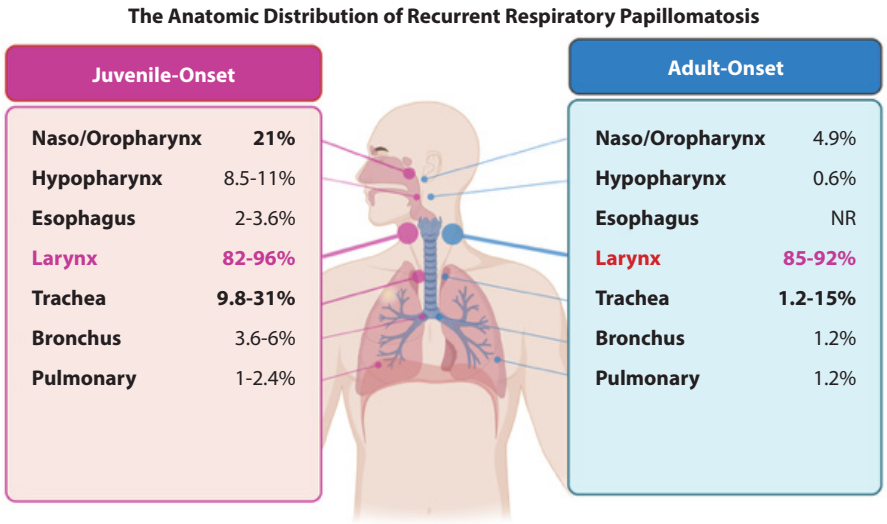

Figure 2A. Patterns of Airway Involvement in Juvenile- and Adult-Onset Recurrent Respiratory Papillomatosis.

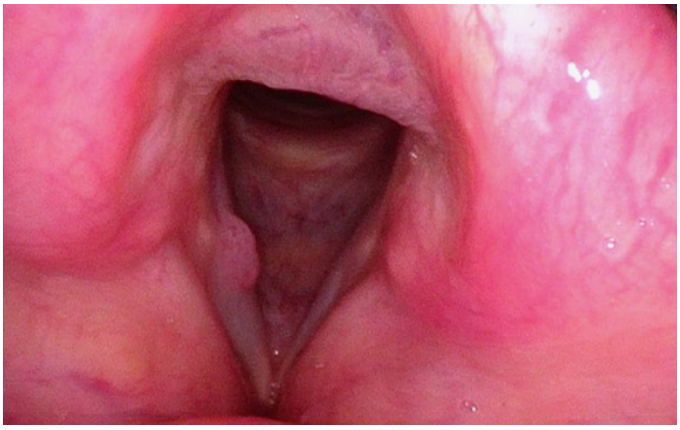

Figure 2B. shows focal laryngeal papillomatosis, demonstrating a solitary discrete papillomatous lesion at the right true vocal cord associated with HPV6 infection.

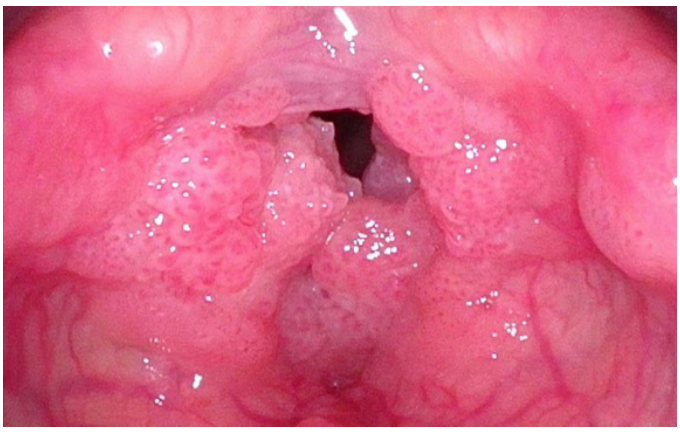

Figure 2C. shows diffuse laryngeal papillomatosis, demonstrating severe papillomatous lesions along the bilateral true vocal cords and false vocal cords related to HPV11 infection.

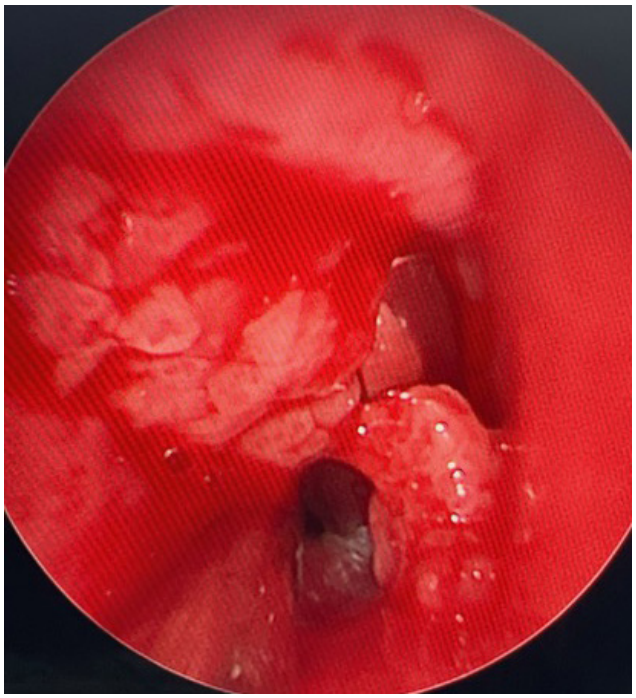

Figure 2D. shows tracheal papillomatosis, demonstrating papillomatous lesions in the suprastomal trachea of a patient post tracheostomy.

Natural History of Recurrent Respiratory Papillomatosis (Table 2)

HPV11 infection is more frequently associated with aggressive RRP phenotypes, characterized by rapid lesion regrowth, earlier disease, multilevel airway involvement, and extension to the tracheobronchial tree or lungs. In contrast, HPV6-associated disease more commonly remains confined to the larynx and follows a slower clinical course. Additionally, the risk of malignant transformation is higher in HPV11-associated disease.[26,27]

Diagnosis

The diagnosis of recurrent respiratory papillomatosis (RRP) necessitates a multifaceted approach that includes clinical history, endoscopic evaluation, histopathological examination, and virologic testing. A thorough clinical history is essential for elucidating symptoms and relevant medical background. Endoscopic procedures, such as flexible or direct laryngoscopy, facilitate the visualization of papillomatous lesions within the larynx, whereas bronchoscopy is warranted when lower airway involvement is suspected. Histopathological analysis of biopsies typically reveals exophytic squamous papillomas characterized by fibrovascular cores. Furthermore, virologic testing through polymerase chain reaction (PCR) can effectively identify specific human papillomavirus (HPV) strains, including HPV-6 and HPV-11, and may possess prognostic implications.

The differential diagnoses for RRP encompass a range of other benign laryngeal lesions, such as granulomas and cysts, as well as various infectious processes and neoplastic conditions. Additionally, the consideration of focal and diffuse central airway diseases is vital. Focal involvement may manifest in association with tracheal neoplasms, lesions of traumatic origin, post-intubation stenosis, certain infectious diseases, and systemic disorders that can result in focal stenosis. In contrast, diffuse involvement may occur in a wide array of conditions, including granulomatosis with polyangiitis, amyloidosis, tracheobronchopathia osteochondroplastica, relapsing polychondritis, tracheobronchomegaly, tuberculosis and other granulomatous infections, neurofibromatosis, and sarcoidosis. This comprehensive diagnostic strategy is imperative for accurately distinguishing RRP from other conditions affecting the airway.[42]

Table 2. Clinical Features of Juvenile-onset and Adult-onset Recurrent Respiratory Papillomatosis.

Category	Juvenile-Onset RRP (JoRRP)	Adult-Onset RRP (AoRRP)
Definition[9,21,28]	Onset before age 12–18 (depending on definition; most use < 12 years)	Onset after age 18
Age at Diagnosis[29,30,31,32]	2–5 years most common	20–40 years (wide range)
Gender Ratio[4,21,30]	Slight male predominance (≈1.1–1.3:1)	Clear male predominance (≈1.5–2:1)
Transmission[21,28,33]	Mostly vertical transmission during childbirth	Horizontal transmissionthrough sexual contact or contact with HPV lesions
HPV Types (Global Estimates)[21,28,33]	HPV-6: ~55–70% HPV-11: ~30–45%	HPV-6: ~55–70% HPV-11: ~30–45%
Clinical Severity[21,28,33]	More severe, more aggressive growth, higher recurrence	Generally less aggressive, slower progression
Frequency of Surgical Debulking[34,35]	High: mean 4–8 surgeries/year, some > 10	Lower: 1–2 surgeries/year
Likelihood of Tracheal or Lung Spread[36,37,38]	Higher risk (2–8%)	Lower (< 1–4%)
Malignant Transformation Risk[39]	~1–4%	Up to 3–7% in some adult cohorts
Course of Disease[28]	Often chronic, relapsing-remitting into adolescence; may stabilize after puberty	Relapsing but more stable; slower progression
Risk Factors[21,28,33]	Vaginal delivery, firstborn, young maternal age	Smoking, sexual behavior, co-infection
Burden on Healthcare[2,40]	Very high: early-onset, repeated anesthesia exposure, impacts speech, schooling	Significant but less disruptive to daily functioning
Impact of HPV Vaccination[14]	Strong evidence of reduced incidence in highly vaccinated regions (Australia, Denmark)	Adult impact is indirect—reduced community circulation
Approved Adenoviral Vactor-based HPV-6/11-targeted Immunotherapy (Papzimeos)[41]	N/A	Yes

Management

There is currently **no definitive cure for recurrent respiratory papillomatosis (RRP)**, and optimal management requires a **multidisciplinary approach** involving otolaryngology, anesthesiology, pulmonology, speech and voice therapy, and, when appropriate, infectious disease specialists. Surgical debulking remains the cornerstone of treatment to maintain airway patency; however, disease recurrence is common and often necessitates repeated interventions.

The recent approval of a first-in-class adenoviral vector–based HPV-6/11–targeted immunotherapy (Papzimeos) represents an important advance in non-surgical management. This immunotherapeutic approach has the potential to modify the natural history of RRP. Based on single-arm phase 1/2 trials, current evidence shows it enables more durable disease control. However, long-term durability beyond reported follow-up remains under investigation. In selected patients, there is a possibility of long-term remission or cure, thereby reducing reliance on repeated surgical procedures.

The primary objectives of RRP management include: Maintaining airway patency and respiratory safety, preserving or restoring voice quality and laryngeal function, reducing papilloma burden and the frequency of surgical interventions, preventing or managing distal airway involvement and related complications

Complications related to disease burden and repeated surgical interventions are common. Extensive or recurrent lesions and cumulative surgical trauma may result in vocal fold scarring, anterior glottic web formation, or glottic/subglottic stenosis, leading to permanent voice impairment. Acute airway compromise remains a potentially life-threatening event requiring prompt intervention. Distal spread to the tracheobronchial tree and lung parenchyma may occur, resulting in multifocal disease that is more difficult to control and associated with increased morbidity.

Although uncommon, malignant transformation to squamous cell carcinoma has been reported in RRP. Potential risk factors include infection with high-risk HPV genotypes, chronic inflammation, and prior radiation therapy. Accordingly, close longitudinal surveillance with regular endoscopic evaluation is essential to monitor disease activity, airway status, and treatment response. Pulmonary surveillance, including imaging and bronchoscopy, should be undertaken when lower airway involvement is suspected.

1. Surgical Management

Surgical intervention remains the primary approach, often involving tumor debulking through microlaryngoscopic excision techniques. These may utilize cold steel or microdebrider instruments, as well as laser ablation techniques such as CO_2 laser or pulsed-dye/KTP laser. The choice of technique can vary based on the surgeon's experience and the specific characteristics of the lesion. This procedure can be repeated as needed when symptoms recur. Airway management strategies, such as tracheostomy, are reserved for cases of upper airway obstruction or in refractory pediatric patients. However, this option may increase the risk of distal spread and necessitate vigilant distal airway monitoring.

2. Pharmacological Management

Pharmacological agents serve as adjuvant treatments aimed at decreasing recurrence and the need for surgery. Indications for pharmacotherapy include rapidly recurring disease, extensive distal spread, high surgical burdens, or unsatisfactory voice and airway outcomes post-surgery.

Cidofovir: Utilized off-label as intralesional injections following debulking. Efficacy reports are mixed, showing some reduction in recurrence, but randomized controlled data are limited. Safety concerns, such as potential nephrotoxicity and theoretical oncogenicity, warrant careful consideration of risks versus benefits.

Interferon-alpha: Historically administered systemically with varied outcomes and significant systemic side effects.

Bevacizumab (anti-VEGF): Emerging as a key treatment option for refractory disease, although most data are observational. Intralesional bevacizumab has shown a reduction in recurrence and extended surgical intervals in several case series. Systemic (IV) administration may be beneficial in severe, refractory, multi-level disease, leading to significant decreases in lesion burden and surgical requirements; however, it necessitates oncological monitoring for systemic adverse effects such as hypertension, thromboembolism, and proteinuria.

Other adjuvants: Various agents, including antiviral medications, mTOR inhibitors, retinoids, photodynamic therapy, and immune modulators, have been tested with inconsistent benefits and limited evidence.

3. Non-Pharmacological Management

Voice therapy and rehabilitation are crucial for functional recovery post-treatment, optimizing vocal function and minimizing compensatory strain.

Mortality

In recently published small-cohort series, mortality ranged from 5% in a single-center JoRRP cohort of 121 children[43] to 16% in 122 patients with RRP involving the lower respiratory tract.[37] Importantly, these studies represent selected high-risk populations and may therefore overestimate mortality for the general RRP population. In a separate JoRRP cohort of 192 children, bronchial and pulmonary involvement was associated with a markedly worse prognosis — including a higher frequency of surgical interventions, a greater need for tracheotomy with failure of decannulation, and a substantially increased mortality rate (OR = 94.9; 1/175 vs 6/17) compared with those without distal airway disease.[27,36]

Prevention

Prophylactic HPV vaccination (e.g., quadrivalent and nanovalent vaccines that include HPV-6 and HPV-11) reduces the incidence of HPV infection with vaccine-covered types and is associated with decreased rates of juvenile-onset RRP in populations with high vaccine uptake. Vaccination of adolescents and young adults prior to HPV exposure is recommended. The role of cesarean delivery solely to prevent vertical transmission is not routinely recommended and should be individualized when maternal genital papillomas are extensive and obstructive.

Recent Advances in HPV-6/HPV-11–Targeted Immunotherapy

Rationale and Development Update (Figure 3, Table 3)

The major drivers of recurrence after surgery are incomplete removal of papillomatous tissue and the persistence of HPV in the surrounding mucosa.[44] Patients with recurrent respiratory papillomatosis exhibit impaired local immune responses that limit their ability to clear HPV-6 or HPV-11 infection. Studies[45,46,47,48] have shown reduced activation of innate immune cells, including Langerhans cells, and defective HPV-specific cellular immunity (polarized to T-helper type 2 or Th2 or regulatory T-cell -Treg responses), contributing to viral persistence. In addition, the papilloma microenvironment demonstrates features of immune tolerance, including regulatory T-cell enrichment and elevated immune-checkpoint signaling, which suppress effective antiviral T-cell responses. These abnormalities create a permissive niche for chronic HPV infection and recurrent lesion growth. (**Figure 3**)

To overcome this challenge of recurrent RRP, three HPV-6/HPV-11–targeted immunotherapeutic platforms have been developed and entered phase 1–2 clinical trials: a gorilla adenoviral vector-based therapy and a DNA plasmid-based vaccine, both encoding the HPV-6/HPV-11 E6/E7 oncogenic proteins; and a Modified Vaccinia Ankara (MVA)-based E2 vaccine. Their aim is to induce strong E6/E7-specific cellular immune responses—particularly $CD8^+$ T-cell responses—to overcome local immunotolerance, eradicate HPV-6/HPV-11–infected cells, and eliminate papillomatous lesions in RRP. (**Table 3**) Beyond these two platforms, no additional HPV-6/HPV-11–specific immunotherapies are currently registered in clinical trials for RRP. Several promising immunotherapeutic modalities—including mRNA-LNP vaccines, peptide/protein vaccines, adoptive T-cell/TCR therapies, and siRNA/antisense oligonucleotide antivirals—are in preclinical or early-phase development primarily for high-risk HPV-16/18–related cancers. Adaptation of these platforms for low-risk HPV-6/11 RRP is biologically plausible and may emerge as the next wave of targeted RRP therapeutics.

1. **Adenoviral vector-based HPV-6/11-targeted Immunotherapy**

   Papzimeos (zopapogene imadenovec-drba; PRGN-2012) **was approved by the U.S. FDA in August 2025 as the first-in-class therapy for adults with recurrent respiratory papillomatosis (RRP).**[41] The developer is Precigen. Papzimeos is a non-replicating gorilla adenovirus vector (gAdeno) encoding HPV-6 and HPV-11 E6/E7 antigens, functioning as a therapeutic vaccine/immunotherapy (referred to by Precigen as a gene therapy).

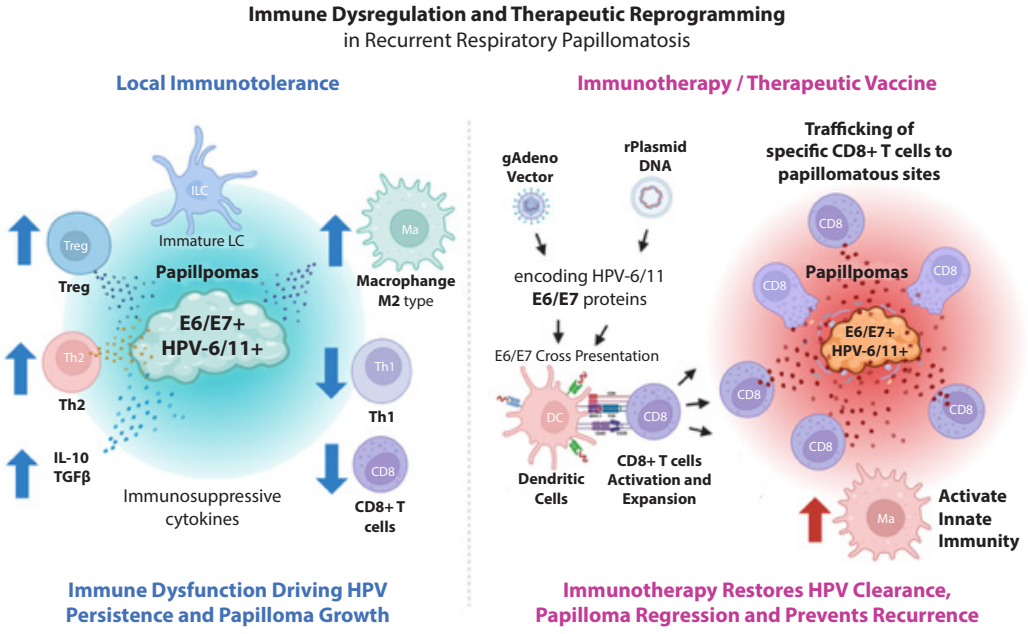

Figure 3. Immune Dysregulation and Therapeutic Reprograming in Recurrent Respiratory Paillomatiosis[45,46,47,48]

Table 3. Summary of HPV-6/HPV-targeted Immunotherapeutic (or Therapeutic Vaccine): for Treatment of Recurrent Respiratory Papillomatosis (RRP)

Agent / Platform	Phase / Status	Population	Intervention	Key Clinical Results
PAPZIMEOS[41,49,50] Gorilla-adenoviral vector -GC46 expressing HPV16/11 E6/E7)	Pivotal single-arm Phase 1/2 **FDA approved** (Aug 2025)	Adults with moderate–severe RRP and reguired ≥ 3 surgeries /year	Subcoutaneous (SC) injections ×4 doses over 12 weeks post-debulking	• 51% (18/35) complete responders (no surgeries at 12 months) • 83% durability at median 36 mo • Surgery reduction: 86% in Year 1; 91% in Year 2; 95% in Year 3 • Well tolerated (mostly Grade 1–2 AEs)
INO-3107[51,52] DNA expressing HPV-6/11 E6/E7	Phase 1/2 completed; Breakthrough Therapy designation	Adults with HPV-6/11 RRP and required ≥ 2 surgeries/year N = 32, male 24. JoRRP 7, AoRRP 25	Imtramuscular (IM) DNA + electroporation (CELLECTRA) on 4-dose schedule	• Safe, highly immunogenic • Complete response 28%, partial response 43.8% • Mean change in total clinical score −11.0 (95% CI −16.7, −5.3) • Reduced surgical frequency • vaccine-induced HPV-specific T-cell clones trafficked to papillomas, correlating with benefit
MVA-E2[58] Modified Vaccinia Ankara expressing E2 gene of bovine papillomavirus	Phase 1/2 (single-arm)	Adults age with RRP (N = 29, age ≥ 18, 18 female, 11 male)	**A Combined intervention:** minimal surgical debulking followed immediately by intralesional MVA-E2 (107 pfu), repeated ×4 times at 2-week intervals	• 44.8% (13/29) complete lesion elimination after primary course • Recurrences in 16/29 (6–18 months), retreated successfully • Acceptable safety
Adjuvant prophylactic HPV vaccines[59] Approved 4 or 9 valents HPV-L1 vaccines that contains HPV-6/11	**Observational cohorts, meta-analyses**	Children & adults post-surgery	Standard prophylactic vaccination schedules	• Consistent reduction in surgery frequency and extended inter-surgical interval in many cohorts • Evidence quality low–moderate (non-randomized), but reproducible signal of clinical benefit

The vector enables in vivo expression of E6/E7 proteins, designed to elicit strong and specific T-cell–mediated immune responses that eliminate HPV-6/11–infected cells. A remark: although the company refers to it as a gene therapy, its mechanism is immunologic correction rather than genetic correction. Therefore, from a scientific standpoint, it is an immunotherapy or therapeutic vaccine. However, because it uses a gene-delivery viral vector, some companies or regulators may still classify it under the gene therapy category.

Approval was based on the results of a single-center, single-arm phase 1/2 clinical trial (NCT04724980).[49] Adults aged ≥ 18 years with RRP requiring ≥ 3 surgical interventions in the preceding 12 months received four adjuvant dosesof PRGN-2012: on Day 1 following surgical debulking, and on Days 15, 43, and 85. Among 35 evaluable patients, 51% (18/35) achieved a complete response, defined as no requirement for any RRP surgery for 12 months following treatment. Overall, 86% of patients demonstrated a significant reduction in surgical frequency, with the median number of surgeries decreasing from 4 per year at baseline to 0 after treatment. PRGN-2012 was generally well tolerated. Most adverse events were mild (Grade 1–2), with the most common being injection-site reactions, fatigue, chills, and fever. However, safety and efficacy have not been established in patients under 18. In addition, long-term follow-up has not been revealed beyond the initial safety profile.

Advantages of the gorilla adenoviral (GC46) vector platform include its very low anti-vector seroprevalence in humans (< 5% in a cohort from United States, 20% in cohorts from Kenya and Ghana) compared with human adenoviral vectors such as hu-Ad5 (> 60%), allowing more efficient vector transduction and strong induction of $CD8^+$ T-cell responses.[50] Of note, the potential for anti-vector immunity, which may limit the effectiveness of future homologous redosing, as well as the extremely rare risk of vector-associated thrombosis observed with some chimpanzee adenoviral vaccines (e.g., ChAdOx), remain unknown for this vector.In addition, because GC46 is a proprietary vector, its restricted availability may limit broader development and could pose challenges for global equitable access. (**Table 3**)

2. DNA-based HPV-6/11-Targeted Immunotherapy

INO-3107 is a recombinant DNA plasmid that encodes HPV-6/11 E6 and E7 proteins. The developer is INOVIO. In a completed single-arm phase 1/2 clinical trial in 32 patients with recurrent respiratory papillomatosis (7 juvenile-onset, 25 adult-onset), INO-3107 was administered by intramuscular injection followed by in vivo electroporation using the CELLECTRA® device on a four-dose schedule.[51,52] The treatment was safe and well tolerated, and it elicited robust immunogenicity.

Twenty-eight percent of patients achieved a complete response, and 43.8% achieved a partial response. The mean change in total clinical severity score was −11.0 (95% CI −16.7 to −5.3). Preliminary analyses indicate that vaccine-induced HPV-specific T-cell clones trafficked to papillomatous lesions, correlating with clinical benefit. The advantgae of the DNA-based platofrm is not affected by pre-existing anti-vector immunity, a potential issue with some viral vector platforms. The limitation of INO-3107 is the requirement of a specialized device (CELLECTRA) for administration, which might be a logistical challenge compared to standard injections. (**Table 3**)

Modified Vaccinia Ankara (MVA)-based Bovine papilomavirus E2 vaccine (named MVA-E2) A recombinant Modified Vaccinia Ankara (MVA) vector expressing the bovine papillomavirus E2 gene has demonstrated, in previous non-randomized clinical studies, the ability to eliminate HPV DNA with regression of high-risk HPV-16/18–associated precancerous lesions, including CIN1/2/3, VIN2/3, and urethral intraepithelial neoplasia.[53,54,55,56,57] In 2019, a phase 1/2 single-arm, open-label trial administered intralesional MVA-E2 to 29 recurrent respiratory papillomatosis (RRP) patients (18 females; 9 juvenile-onset; aged 18 months–65 years; prior surgery 1–16 times). The study reported that 44.8% (13/29) achieved complete remission. Patients who experienced recurrence received a second treatment and subsequently remained recurrence-free for 3–8 years.[58] It is important to note, however, that the intervention in this trial combined intralesional MVA-E2 administration with four coordinated sessions of minimal surgical debulking, a strategy that may pose practical challenges for broader adoption in real-world clinical practice. (**Table 3**)

3. Approved HPV Prophylactic Vaccine as an Adjunct Therapy for RRP

Approved HPV prophylactic vaccines containing L1 antigens of HPV-6/11 genotypes—including the quadrivalent and nanovalent vaccines—were originally designed purely for prevention. However, accumulating case reports and retrospective series suggest that these vaccines may confer clinically meaningful therapeutic benefit in Recurrent Respiratory Papillomatosis (RRP), including reduced recurrence rates, prolonged remission intervals, and, in rare instances, complete disease regression.

One retrospective cohort of 24 patients compared 13 individuals vaccinated with the quadrivalent HPV-6/11/16/18 vaccine (Gardasil) with 11 unvaccinated controls over long-term follow-up (1990–2012). Among the vaccinated group, only 2 of 13 (15.4%) experienced recurrence over an approximate mean of 55 months, whereas all 11 unvaccinated patients (100%) relapsed over an approximate mean of 12.3 months.[59,60]

In 2023, two meta-analyses (n = 243 and n = 101 patients, respectively) further consolidated this evidence.[59,60] The larger analysis demonstrated a mean reduction of 4.43 surgeries per year after vaccination (95%CI: −7.48 to −1.37) and a mean increase in inter-surgical interval of 15.73 months (95%CI: 1.46–29.99).[59] The second analysis showed an overall reduction of 0.123 recurrences or surgeries per month (95%CI: 0.064–0.183).[60] Together, these findings support the conclusion that HPV prophylactic vaccination may serve as a beneficial adjunct therapy alongside surgical management of RRP. (**Table 3**)

Given the favorable safety profile of HPV vaccines and the substantial morbidity associated with repeated surgical interventions, adjuvant HPV vaccination is increasingly considered justifiable as current best-practice, particularly in settings where the newly approved Papzimeos is unavailable or unaffordable. The mechanistic basis for this therapeutic effect remains speculative, although proposed explanations include antibody-mediated prevention of reinfection and augmentation of host antiviral immunity.

Prospective multicenter studies, ideally randomized, or at minimum well-controlled cohort designs, are still needed to confirm efficacy, refine timing and dosing strategies, and elucidate relevant immunologic correlates. In addition, currently, neither Papzimeos nor INO-3107 has received regulatory approval for use in pediatric patients with recurrent respiratory papillomatosis. The absence of pediatric approval reflects important scientific and safety uncertainties, including the lack of data on viral or plasmid vector performance in younger age groups, where tissue distribution, transgene expression, and immune activation may differ substantially from adults. Moreover, the immunologic milieu in aggressive juvenile-onset RRP is increasingly recognized as distinct from adult-onset disease, with differences in innate and adaptive immune responses, viral persistence, and inflammatory regulation. These age-related biological differences raise concerns regarding extrapolation of adult efficacy and safety data to children and underscore the need for dedicated pediatric studies before these immunotherapeutic approaches can be considered for routine use in juvenile RRP.

Conclusion

Recurrent respiratory papillomatosis is a rare, chronic HPV-driven disease of the airway associated with substantial morbidity due to recurrent lesion growth, airway obstruction, and voice impairment. Current management relies primarily on repeated surgical debulking, with adjuvant medical therapies reserved for refractory disease. Widespread implementation of prophylactic HPV vaccination targeting HPV-6 and HPV-11 has led to a reduction in disease incidence. The recent approval of the first-in-class adenoviral vector–based HPV-6/11–targeted immunotherapy (Papzimeos) represents a potential paradigm shift from repeated surgical intervention toward durable,

immune-mediated disease control. Continued research into antiviral, immunologic, and targeted therapeutic strategies is essential to further improve long-term outcomes for patients with RRP.

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