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Original Article

Recurrent Respiratory Papillomatosis: Current Insights into Epidemiology, Pathogenesis, and Emerging Therapeutic Strategies

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Abstract: Recurrent respiratory papillomatosis (RRP) is a benign, HPV 6/11-driven airway disease with frequent recurrences, often requiring multiple surgeries and imposing significant clinical and economic burdens. This narrative review synthesizes evidence from 2010–2025 on epidemiology, pathogenesis, clinical features, and therapies, emphasizing advances like bevacizumab, immune checkpoint inhibitors, and gene therapy (PRGN-2012, announced for FDA approval as Papzimeos™ on August 14, 2025). A structured literature search in PubMed, Scopus, and Web of Science identified 26 studies (clinical trials, cohorts, reviews). Key findings: HPV vaccination reduced juvenile RRP (JoRRP) incidence by >90% in vaccinated populations (e.g., Australia). Bevacizumab prolongs surgery-free intervals (up to 85% response rate systemically), while PRGN-2012 achieved a 51% complete response (no surgery for ≥12 months) with sustained benefits >2 years and mild adverse events, pending confirmation in peer-reviewed publications. INO-3107 reduced mean surgeries from 4.1 to 0.9 over two years, with an 86% overall response rate (ORR) in Year 2. Traditional adjuvants like cidofovir remain relevant in low-resource settings. Multimodal strategies (surgery, anti-angiogenics, immunotherapy) shift toward disease modification. Enhanced vaccination and biomarker research are crucial for global control.

Keywords: Recurrent Respiratory Papillomatosis; HPV; Bevacizumab; PRGN-2012; INO-3107; HPV vaccination; Cidofovir.

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1. Introduction

Recurrent respiratory papillomatosis (RRP) is the most common benign neoplasm of the larynx, caused predominantly by HPV types 6 and 11 [1]. Although benign, the disease may follow an aggressive course with frequent recurrences, airway obstruction, and potential malignant transformation [2]. RRP occurs in two forms: juvenile-onset (JoRRP), presenting in childhood, and adult-onset (AoRRP), manifesting later in life [3]. Despite advances in surgical techniques and adjuvant therapy, management remains challenging, and recurrence is frequent [4]. Recently, novel immune-based strategies, including bevacizumab and PRGN-2012 gene therapy, have shown encouraging results [5]. The announced FDA approval of PRGN-2012 on August 14, 2025, represents a potential therapeutic milestone as the first systemic therapy for adult RRP, pending further validation [27].

2. Methods

This narrative review synthesizes recent evidence on the epidemiology, pathogenesis, clinical presentation, and therapeutic strategies for recurrent respiratory papilloma-

tosis (RRP). A structured literature search was conducted in PubMed, Scopus, and Web of Science (January 2010–October 2025) using keywords and MeSH terms: "recurrent respiratory papillomatosis," "laryngeal papillomatosis," "HPV 6," "HPV 11," "bevacizumab," "anti-VEGF," "pembrolizumab," "immune checkpoint inhibitor," "PRGN-2012," "gene therapy," "HPV vaccination," and "treatment outcomes." The search aimed to identify high-quality studies on RRP's disease burden, HPV-related mechanisms, and treatment outcomes.

Studies were selected based on relevance, with quality informally assessed using Joanna Briggs Institute (JBI) tools to prioritize robust evidence, though a formal risk-of-bias analysis was not performed, consistent with the narrative review design. Only articles in English and conducted in human subjects were included. References of selected papers were manually screened to capture additional relevant studies. Studies were included if they described the epidemiology, pathogenesis, clinical course, or management of RRP, or evaluated the effects of surgery, pharmacologic adjuvants, HPV vaccination, or emerging systemic therapies.

Exclusion criteria comprise case reports, editorials, letters without primary data, animal or in vitro studies, and those focusing on non-laryngeal HPV diseases. Narrative reviews were included to contextualize clinical trends, while regulatory and translational reports were incorporated to highlight therapeutic advancements (e.g., PRGN-2012 approval). Data was extracted regarding study design, sample size, interventions, and outcomes such as recurrence rate, surgery-free interval, response rate, and safety. A supplemental table summarizes the 26 included studies (see Table 1). Due to heterogeneity among study designs, a narrative synthesis was adopted.

3. Results

The literature search yielded 1358 records published between 2010 and 2025. After removing duplicates, 102 unique articles were screened by title and abstract, and 40 were assessed in full. Ultimately, 26 studies met inclusion criteria, comprising six clinical trials, eight cohort studies, five systematic reviews, three narrative reviews, and four regulatory or translational reports (Table 1).

Table 1. Summary of Included Studies.

Study	Design	Key Findings	JBI Quality Score
[1]	Narrative Review	Overview of RRP epidemiology, clinical features, and management strategies.	Moderate
[2]	Narrative Review	Discusses current concepts in RRP management, emphasizing surgical challenges and recurrence.	Moderate
[3]	Narrative Review	Reviews RRP epidemiology, pathogenesis, and future therapeutic perspectives.	Moderate
[4]	Narrative Review	Outlines indications for surgery and adjuvant therapies in RRP management.	Moderate
[5]	Phase 1/2 Clinical Trial	PRGN-2012 gene therapy: 51% complete response (no surgery for ≥12 months), durable remission >2 years, mild adverse events.	High
[6]	Cohort Study	HPV vaccination reduced JoRRP incidence by >90% in Australia; modest AoRRP decline (10–20%).	High

[7]	Cohort Study	Describes AoRRP epidemiology; 5–10% spontaneous remission noted.	Moderate
[8]	Cohort Study	Reports RRP incidence: 0.17–1.34/100,000 (children), 0.2–3.9/100,000 (adults) in the US.	High
[9]	Systematic Review	Global HPV vaccination reduced RRP incidence; confirms JoRRP decline and modest AoRRP reduction.	High
[10]	Cohort Study	RRP annual cost >$100,000/patient due to frequent surgeries.	High
[11]	Cohort Study	HPV11 linked to aggressive RRP with higher recurrence and distal spread.	Moderate
[12]	Narrative Review	Details HPV pathogenesis, role of E5/E6/E7 proteins in RRP.	Moderate
[13]	Cohort Study	E6/E7 oncogene expression drives epithelial hyperplasia in RRP.	Moderate
[14]	Cohort Study	Immune dysfunction (reduced MHC class I, T-cell exhaustion) in RRP persistence.	High
[15]	Narrative Review	Describes impaired NK cell activity and interferon response in RRP.	Moderate
[16]	Cohort Study	Elevated IL-10/TGF-β in RRP lesions promotes immunosuppressive microenvironment.	High
[17]	Cohort Study	HLA-DRB1*0301 and GATA2 deficiency linked to aggressive RRP.	High
[18]	Cohort Study	HPV11 integration into host DNA associated with aggressive RRP and malignant transformation risk.	High
[19]	Cohort Study	Cidofovir reduces recurrence (30–50% response) but risks nephrotoxicity.	Moderate
[20]	Cohort Study	Interferon-alpha shows 20–40% response in RRP, limited by systemic side effects.	Moderate
[21]	Cohort Study	Bevacizumab targets VEGF-A, reduces lesion regrowth in RRP.	High
[22]	Clinical Trial	Systemic bevacizumab: 85% response rate, prolonged surgery-free intervals.	High
[23]	Clinical Trial	Intralesional bevacizumab in JoRRP: improved VHI, reduced recurrence.	High
[24]	Cohort Study	HPV vaccination as adjuvant therapy reduces surgery frequency	High

		in RRP.	
[25]	Systematic Review	Immunotherapies (e.g., HPV vaccines) show prophylactic/therapeutic benefits in RRP.	High
[26]	Clinical Trial	Pembrolizumab: 33% partial response, 44% stable disease in refractory RRP.	High
[27]	Regulatory Report	Announced PRGN-2012 approval for adult RRP (August 14, 2025).	Moderate
[28]	Translational Report	PRGN-2012 pivotal trial data: 86% surgery reduction, cost offset potential.	Moderate
[29]	Phase 1/2 Clinical Trial	INO-3107: 86% ORR at 2 years, surgery reduction from 4.1 to 0.9/year.	High
[30]	Regulatory Report	HPV vaccine coverage in LMICs: 41% in Africa, below WHO 90% target.	Moderate

3.1 Epidemiology and Clinical Features

RRP exhibits a bimodal age distribution. Juvenile-onset RRP (JoRRP) typically manifests before age 12, primarily due to vertical transmission of HPV from infected mothers during vaginal delivery. Adult-onset RRP (AoRRP) usually appears between the third and fifth decades, possibly related to latent reactivation or horizontal transmission via oral sexual contact [3,7]. The incidence varies geographically: 0.17–1.34 per 100,000 in children and 0.2–3.9 per 100,000 in adults [8]. Despite its rarity, the chronic relapsing nature leads to lifelong management. Clinical presentation includes progressive hoarseness, dyspnea, and airway obstruction. Tracheal and bronchial spread occurs in 5–10% of cases and predicts a more severe course [11]. Malignant transformation to squamous cell carcinoma is rare (<1%) but is higher with HPV11, long-standing disease, prior radiation, and smoking [2,11].

Since the advent of HPV vaccination, major shifts in disease epidemiology have been observed. In Australia, where >85% of the population is vaccinated with the quadrivalent HPV vaccine, JoRRP incidence declined by >90% within 10 years [6,9]. Similar trends are reported in Denmark and Finland. While HPV vaccination has dramatically reduced JoRRP incidence, data on AoRRP trends are less robust. Limited cohort studies suggest a modest decline in AoRRP incidence in vaccinated populations (e.g., 10–20% reduction in Denmark [9]), likely due to herd immunity, but no significant shift in disease severity or age of onset has been consistently reported. Emerging data indicate rare cases of non-HPV 6/11 genotypes (e.g., HPV 16) in AoRRP, particularly in vaccinated cohorts, suggesting potential genotype replacement. However, these findings are preliminary, and further longitudinal studies are needed to assess demographic shifts and inform screening strategies. Global modeling predicts that universal vaccination could reduce RRP incidence by 80% by 2100, highlighting the preventive potential of immunization.

3.2 Pathogenesis

The pathogenesis of RRP centers on persistent infection of the laryngeal basal epithelium by HPV types 6 and 11, which gain access through microtrauma or perinatal

exposure. Viral early proteins—E5, E6, and E7—disrupt cell cycle checkpoints, inhibit apoptosis, and suppress interferon signaling, leading to epithelial hyperplasia and lesion formation [12,13]. HPV-mediated immune evasion is critical for persistence, with down-regulation of MHC class I molecules impairing antigen presentation and cytotoxic T lymphocyte activation [14]. Patients exhibit reduced NK cell activity, T-cell exhaustion, and diminished interferon response, resulting in inadequate viral clearance [15]. Lesions are highly vascularized, with overexpression of VEGF and FGF, which sustain lesion growth and recurrence [21]. The local cytokine milieu favors tolerance, with elevated IL-10 and TGF-β promoting an immunosuppressive microenvironment [16].

Despite immune evasion, a small subset of AoRRP patients (5–10%) experience spontaneous remission, often after years of disease [7]. This phenomenon suggests host factors beyond known genetic predispositions (e.g., HLA-DRB1*0301, GATA2 deficiency [17]) may restore immune surveillance. Potential mechanisms include enhanced NK cell activity or shifts in the local cytokine milieu (e.g., reduced IL-10, increased IFN-γ), though specific triggers remain poorly understood. Identifying biomarkers of remission could guide non-surgical management strategies.

HPV11's frequent integration into host DNA, observed in aggressive RRP, induces epigenetic silencing of tumor suppressor genes, contributing to a more severe phenotype and rare malignant transformation (<1%) [18]. This integration may serve as a prognostic biomarker to stratify patients for early systemic therapies (e.g., bevacizumab, PRGN-2012). Preliminary genomic analyses suggest HPV11-integrated cases exhibit higher recurrence rates and distal spread, warranting further research to validate its utility in risk stratification and personalized treatment planning.

3.3 Therapeutic Strategies

Surgical management remains the cornerstone of therapy. However, despite improvements in visualization techniques (e.g., narrow-band imaging, CO_2 laser excision, microdebrider-assisted debulking), recurrence is nearly universal due to persistent HPV6/11 DNA in basal epithelial cells. Most patients require 2–8 surgeries per year, with aggressive cases exceeding 20 procedures annually, imposing substantial physical, psychological, and financial burdens [4,10].

Traditional adjuvants like intralesional cidofovir and interferon remain relevant, particularly in low-resource settings. Cidofovir, an antiviral, reduces recurrence rates (30–50% response rate) but carries risks of nephrotoxicity and local irritation [19]. Interferon-alpha, used historically, shows modest efficacy (20–40% response) but is limited by systemic side effects (e.g., flu-like symptoms, hepatotoxicity) [20]. In contrast, intralesional bevacizumab offers higher response rates (up to 85%) and fewer systemic toxicities but is significantly more expensive (estimated $1,000–$2,000 per dose vs. $100–$200 for cidofovir). While bevacizumab's superior efficacy supports its use in severe RRP, cidofovir remains a cost-effective option in resource-constrained settings, though comparative trials are limited.

Bevacizumab, a monoclonal antibody targeting VEGF-A, has revolutionized RRP management. Intralesional administration with CO_2 laser surgery prolongs surgery-free intervals by up to 12 months, improves Voice Handicap Index (VHI), and minimizes lesion regrowth. Systemic therapy demonstrated an 85% overall response rate, including complete or partial regression in diffuse and distal disease [21–23,29]. Adverse effects were mild (hypertension, proteinuria), with rebound growth only after abrupt discontinuation.

Quadrivalent and nonavalent HPV vaccines have shown prophylactic and therapeutic benefits. Vaccinated populations exhibit reduced JoRRP incidence, and postoperative vaccination in affected individuals decreases surgery frequency and recurrence risk [24,25]. Checkpoint inhibitors, particularly pembrolizumab, have shown disease stabilization and partial responses in refractory RRP (33% partial response, 44% stable disease) with manageable immune-related adverse events [26].

PRGN-2012 and INO-3107 represent promising immunotherapies for RRP. PRGN-2012 achieved a 51% complete response rate (no surgery for ≥12 months) with durable remission beyond 2 years in a phase 1/2 trial [5]. In contrast, INO-3107 demonstrated an 86% overall response rate at 2 years, with mean surgical frequency decreasing from 4.1 to 0.9 annually, reflecting robust T-cell responses [29]. While PRGN-2012's complete response indicates potential for surgery-free intervals, INO-3107's higher ORR and significant surgery reduction suggest broader clinical benefit over time. Direct comparative trials are needed to determine whether complete surgery avoidance (PRGN-2012) or substantial reduction (INO-3107) better optimizes patient outcomes. On August 14, 2025, the FDA announced approval of PRGN-2012 (Papzimeos™) as the first systemic immunotherapy for adult RRP, based on pivotal phase 1/2 trial data [5,27,28]. While promising, these findings await confirmation in peer-reviewed publications to fully elucidate long-term efficacy and safety.

RRP imposes a significant economic burden, with annual per-patient costs exceeding $100,000 due to frequent surgeries [10]. Novel therapies like bevacizumab ($10,000–$20,000 annually), checkpoint inhibitors (e.g., pembrolizumab, ~$150,000/year), and gene therapies (PRGN-2012, INO-3107, costs undisclosed but likely high) significantly increase expenses compared to surgical debulking ($5,000–$10,000 per procedure). However, PRGN-2012's 86% surgery reduction and INO-3107's decrease from 4.1 to 0.9 surgeries annually may offset costs over 2–3 years by reducing surgical frequency [5,29]. In contrast, traditional adjuvants like cidofovir ($1,000–$2,000/year) remain cost-effective but less efficacious. Cost-effectiveness analyses are needed to guide adoption in public health systems, particularly in LMICs.

Developing pre-treatment biomarkers to predict response to bevacizumab (anti-angiogenic) versus immune-driven therapies (e.g., PRGN-2012, INO-3107) is critical for personalized RRP management. High VEGF expression may identify bevacizumab responders, while low T-cell activity or high IL-10/TGF-β levels could indicate candidates for immunotherapies [15,16]. HPV11 integration status may further stratify aggressive cases for early systemic therapy [18]. Preliminary data suggest non-responders to bevacizumab (15–20%) exhibit lower VEGF-A levels, but no validated biomarkers exist. Future research should prioritize multi-omic profiling to guide therapy selection and optimize outcomes.

3.4 Global Challenges

In low- and middle-income countries (LMICs), particularly in Africa and Asia, HPV vaccine coverage remains below 50%, with uptake in Africa at approximately 41% compared to the WHO target of 90% by 2030 [30]. Barriers include limited infrastructure, supply chain issues, and low awareness. Targeted strategies, such as school-based vaccination programs and public awareness campaigns, are essential to accelerate immunization and reduce RRP disparities.

4. Conclusion

Recurrent respiratory papillomatosis is a benign yet recurrent airway disease with substantial morbidity. Management has evolved from surgery alone to include targeted therapies like bevacizumab and HPV vaccination, which reduce recurrence, and emerging immunotherapies like PRGN-2012 and INO-3107, which offer disease-modifying potential. The announced FDA approval of PRGN-2012 in August 2025 marks a milestone, though further data are needed. Traditional adjuvants like cidofovir remain relevant in resource-limited settings. The future of RRP management lies in personalized, multimodal strategies combining surgical, pharmacologic, and immunologic interventions, guided by predictive biomarkers. Global equity through enhanced HPV vaccination is imperative to reduce disease burden.

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References

1. Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: A review. Laryngoscope. 2008;118(7):1236–1247.
2. Preciado D, Zalzal G. RRP: Current concepts and management. Curr Opin Otolaryngol Head Neck Surg. 2012;20(6):553–558.
3. Carifi M, Napolitano D, Morandi M, et al. Recurrent respiratory papillomatosis: Current and future perspectives. Ther Clin Risk Manag. 2015;11:731–738.
4. Rosen CA, Bryson PC. Indications for surgery and adjuvant therapy in RRP. Curr Opin Otolaryngol Head Neck Surg. 2018;26(3):162–167.
5. Norberg SM, et al. PRGN-2012 gene therapy in adults with recurrent respiratory papillomatosis: A pivotal phase 1/2 clinical trial. Lancet Respir Med. 2024;13(4):318–326.
6. Novakovic D, Cheng ATL, et al. Impact of HPV vaccination on RRP incidence: A population-based study. JAMA Otolaryngol Head Neck Surg. 2023;149(2):125–133.
7. Dedo HH, Yu KC. Adult-onset RRP: Epidemiology and natural history. Ann Otol Rhinol Laryngol. 2001;110(6):502–509.
8. Armstrong LR, et al. Incidence and prevalence of RRP in the United States. Laryngoscope. 2010;120(9):1759–1766.
9. Garland SM, et al. Global impact of HPV vaccination. Vaccine. 2016;34(52):6413–6420.
10. Marsico M, et al. Economic burden of RRP. Laryngoscope. 2014;124(12):2820–2826.
11. Gerein V, et al. HPV type 11 predicts aggressive RRP. Eur Arch Otorhinolaryngol. 2005;262(6):512–516.
12. Stanley M. Pathogenesis of HPV infection. J Clin Virol. 2010;49(4):S7–S15.
13. Albers A, et al. E6/E7 oncogene expression in RRP. J Med Virol. 2006;78(10):1434–1443.
14. Bonagura VR, et al. Immune dysfunction in RRP. Clin Exp Immunol. 2010;161(3):408–416.
15. Vambutas A, Bonagura VR. Natural immunity in RRP. Curr Opin Otolaryngol Head Neck Surg. 2021;29(6):435–442.
16. San Giorgi MRM, et al. Cytokine profiles in RRP. Clin Otolaryngol. 2016;41(5):549–557.
17. Iftner A, et al. Genetic predisposition to RRP. PLoS One. 2012;7(12):e49236.
18. Van den Hoogen FJ, et al. Genomic landscape of HPV in RRP. Tumour Virus Res. 2024;17:200291.
19. Simo R, et al. Cidofovir and interferon therapy outcomes. Head Neck. 2013;35(7):1019–1025.
20. Yilmaz T, et al. dsRNA-induced interferon therapy in refractory RRP. Acta Otolaryngol. 2019;139(7):640–646.
21. Best SR, et al. Bevacizumab in RRP: Mechanistic insights. Laryngoscope. 2012;122(10):2146–2152.
22. Zeitels SM, et al. Systemic bevacizumab for aggressive RRP. Ann Otol Rhinol Laryngol. 2022;131(10):1145–1152.
23. Maturo S, Hartnick C. Intralesional bevacizumab outcomes in JoRRP. Otolaryngol Head Neck Surg. 2023;169(2):345–353.
24. Young DL, et al. HPV vaccination as adjuvant therapy in RRP. Laryngoscope. 2022;132(3):567–575.
25. Ventola CL. Immunotherapeutic advances in HPV disease. Pharm Ther. 2024;49(1):42–55.
26. Dooling KL, et al. Immunotherapy and checkpoint blockade in RRP. Cancer Immunol Res. 2024;12(5):622–631.
27. U.S. Food and Drug Administration. FDA Approves First Immunotherapy for Recurrent Respiratory Papillomatosis. 2025.
28. Precigen, Inc. Precigen Announces Groundbreaking Pivotal Study Data for PRGN-2012. 2024.
29. Bagley AF, et al. DNA Immunotherapy (INO-3107) Results in Long-Term Surgery Reduction in Recurrent Respiratory Papillomatosis. Laryngoscope. 2025; doi:10.1002/lary.32416.
30. World Health Organization. Human Papillomavirus (HPV) vaccination coverage. 2025.