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The Efficacy of Human Papillomavirus Vaccination as an Adjuvant Therapy in Recurrent Respiratory Papillomatosis

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Abstract

Objective: To characterize the efficacy of human papillomavirus (HPV) vaccination as an adjuvant therapy in recurrent respiratory papillomatosis (RRP).

Data Sources: PubMed, Embase, Cochrane, Google Scholar, ClinicalTrials.gov, and Web of Science databases were queried for articles published before April 2021.

Review Methods: All retrieved studies ($n = 870$) were independently analyzed by two reviewers according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement using predefined inclusion and exclusion criteria. 13 studies met inclusion criteria. A random-effects meta-analysis was performed to study intersurgical interval (ISI) and number of surgical procedures per year before and after vaccination.

Results: The systematic review included 13 studies, comprising 243 patients. All studies utilized the Gardasil® quadrivalent vaccine, and one study (Yiu et al. 2019) utilized both the quadrivalent and Gardasil® 9-valent vaccines. Our meta-analysis included 62 patients with ISI data across 4

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Level of Evidence: NA

studies, and 111 patients with data on the number of surgical procedures per month across 7 studies. The mean number of surgical procedures decreased by 4.43 per year after vaccination (95% CI, −7.48 to −1.37). Mean ISI increased after vaccination, with a mean difference of 15.73 months (95% CI, 1.46–29.99). Two studies reported on HPV sero-conversion, with HPV seropositivity of 100% prior to vaccination and 25.93% after vaccination.

Conclusion: The addition of HPV vaccination was associated with an increase in time between surgeries and reduction in the number of surgical procedures required. HPV vaccination may be a beneficial adjuvant treatment for RRP.

Keywords

human papillomavirus recombinant vaccine quadrivalent; types 6; 11; 16; 18; laryngeal papilloma; papilloma-virus vaccines; recurrent; recurrent respiratory papillomatosis; respiratory papillomatosis

INTRODUCTION

The use of human papillomavirus (HPV) vaccination as an adjuvant therapy in the treatment of recurrent respiratory papillomatosis (RRP) is controversial. Most cases of RRP have been linked to HPV strains 6 and 11, with HPV 11 coinciding with a more aggressive disease course.[1] RRP has been divided into juvenile-onset and adult-onset, defined as onset before or after 18 years of age. Juvenile-onset is hypothesized to result from the transmission of viral secretions at birth during vaginal delivery in mothers infected with genital HPV. The etiology of adult-onset RRP is less understood, whether developing because of sexual transmission or reactivation of latent virus.[1]

RRP is characterized by its unpredictable and variable clinical course, with the mainstay of therapy centered around surgical excision of exophytic lesions. Surgical methods include cold instrumentation, microdebridement, or laser ablation. Many patients require numerous procedures, and some require over 100 interventions to maintain a patent airway and vocalization.[2] Multiple surgical procedures have been associated with irreversible laryngeal damage and impaired quality of life in patients with RRP.[3]

The incidence of RRP is approximated to be 4.3 per 100,000 children and 1.8 per 100,000 adults.[4] The economic burden associated with this disease is disproportionally high because most patients require multiple procedures, with an estimated annual cost between $40–123 million.[5] Due to the significant impact on quality of life and the economic burden of RRP, prevention and adjuvant therapies to improve patient outcomes are critical.

The first HPV vaccine (Cervarix®) targeting high-risk HPV strains 16 and 18 was introduced to the United States in 2004. Subsequently, a quadrivalent vaccine (Gardasil®), targeting subtypes 6, 11, 16, and 18, was introduced in 2006. Most recently, a 9-valent HPV vaccine (Gardasil®9), additionally targeting 5 oncogenic subtypes 31, 33, 45, 52, and 58, has been made available. The advent of HPV vaccination has been linked to significant reductions in the incidence of HPV-related diseases, including RRP.[6]

Few studies have examined the use of HPV vaccine as an adjuvant therapy in the treatment of RRP. Case reports have shown increased intersurgical interval and complete remission.[7–10] Another case report demonstrated that HPV vaccination as an adjuvant therapy for CO2 laser excision resulted in remission of the disease for 6 years after surgery.[11]

Several single-institution cohort studies have observed mixed results with the use of HPV vaccination. Although some studies have demonstrated increased intersurgical interval (ISI), remission, and serum antibody titers with the use of HPV vaccination,[12–15] other studies have failed to demonstrate a significant therapeutic benefit.[16] Due to the relatively low prevalence of RRP, single institution studies are often underpowered to study associations between HPV vaccination and patient outcomes. A prior systematic review in 2019 examined the use of HPV vaccination as an adjuvant therapy in RRP.[25] This prior study found that surgical procedures per month decreased, and ISI increased in RRP patients after vaccination. Our study aimed to include new data sets that have been published since this study to increase the statistical power by utilizing a larger sample size for the meta-analysis. This study aimed to estimate the efficacy of HPV vaccination in the treatment of RRP by conducting a systematic literature review and meta-analysis.

METHODS

Systematic Literature Search

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Before beginning the systematic review, the aim and study protocol were published online using PROSPERO (CRD42021246833). The study was designed based on PICOS criteria. The population was patients with RRP, intervention was Gardasil quadrivalent or nine-valent vaccine, comparison was patient course prior to vaccination, outcome was efficacy as an adjuvant therapy to surgery, and study design included randomized control trials, case control studies, or case series with five or more patients.

The search strategy was developed with, and performed by, a scientific librarian. The following electronic databases were searched: PubMed, Embase.com, Web of Science Core Collection which includes the years 1985-present; and Cochrane-Ovid Platform (i.e., Cochrane Database of Systematic Reviews which include the years 2005-present and Cochrane Central Register of Controlled Trials from inception to the present) until April 12, 2021 (date last searched). Search terms were searched both as controlled vocabulary (MeSH for PubMed and Emtree terms for Embase) for Recurrent Respiratory Papillomatosis (RRP) and Human Papillomavirus (HPV) Vaccine, and as all available free text in the title and/or abstract. The search was restricted to human studies and English language only. No limits were set on year of publication. A topic search was conducted in Web of Science. To minimize publication bias, a search through ClinicalTrials.gov was conducted to identify unpublished relevant trials. In addition, the first 50 references from Google Scholar were downloaded. Further details on the search strategy are shown in Appendix A.

Studies identified by literature search were consolidated using EndNote™ software (version 20; Thompson Reuters), and duplicates were manually removed. Two authors (A.P. and M.C. A.) assessed eligibility by reviewing all abstracts based on inclusion and exclusion criteria. Non-relevant articles were excluded. In case of doubt, the article proceeded to the next pass of review. Any discrepancies were resolved by discussion. The full text was then reviewed for relevant articles. When unable to access full text, an attempt to contact the corresponding author was made.

Eligibility Criteria

Studies were included in the systematic review if the study population included patients with a definitive diagnosis of RRP. The intervention of interest was quadrivalent or 9-valent HPV vaccination. Outcomes of interest included ISI, number of surgeries per year, recurrence, HPV status, and antibody titer before and after vaccination. Studies were included if they involved five or more patients.

Studies were excluded from systematic review if they did not report on surgical outcomes. Articles published in languages other than English, abstract-only articles, conference abstracts, posters, case-reports (defined as <5 patients), reviews, and editorials were excluded. Publications were included if they provided sufficient data on patient demographics, as well as surgical procedures, or ISI before and after HPV vaccination. To be included in the meta-analysis, all studies required at least 1 companion study reporting similar outcomes.

Risk of Bias Assessment

Risk of bias was assessed in all publications selected for full-text review with a modified Newcastle-Ottawa quality assessment scale (available online). Studies were graded between 1 and 9, and assigned to low-, medium-, and high-quality groups. Low quality was defined as scores of 0–3, medium quality as scores of 4–6, and high quality as scores of 7–9. The analysis included medium- and high-quality studies only.

Data Collection and Synthesis of Results

A data extraction form was constructed, and data extraction was then performed by two reviewers (A.P. and E.A.) with any discrepancy resolved through discourse. Demographic data collected included the number of patients, gender, RRP onset (juvenile or adult), mean age at time of diagnosis, HPV subtype, and duration of observation period prior to and after vaccination. The number of patients who received prior adjuvant therapy, including bevacizumab, acyclovir, indole-3-carbinol, and cidofovir, was also collected.

Individual patient outcomes of ISI and the number of surgical procedures per year prior to and after vaccination were collected. Surgical procedures were defined as operating room cases. In studies with missing data, two attempts were made to contact the corresponding author. We received unpublished data sets on individual patient outcomes from Chirila et al.[17] and Tjon Pian Gi et al.[3] Given the limited sample size of RRP, we included these data sets to include a larger sample of patients.

Statistical Analysis

The outcomes of interest were ISI and number of surgical procedures per year before and after vaccination. First-stage statistical analysis calculated the mean difference and corresponding 95% confidence interval (CI) of these outcomes before and after vaccination in individual studies. Second-stage analysis was a random-effects meta-analysis of eligible studies. Of the 13 studies included in the systematic review, 4 studies were eligible for ISI analysis, and 7 studies were eligible for surgical procedures per year analysis. Heterogeneity across studies was tested using the Higgins I^2 statistic. p-values <0.05 were considered statistically significant for all variables of interest.

RESULTS

Systematic Review

A systematic literature search yielded 870 studies. A flow diagram of the search strategy is depicted in Figure 1. Initial review by title and abstract narrowed relevant literature to 35 studies, of which 9 studies did not have a relevant full-text articles available. Based on this study's inclusion and exclusion criteria, 13 studies were identified and considered medium or high-quality by Newcastle-Ottawa quality assessment and were included in the systematic review (Table I).

Random-Effects Meta-Analysis

Individual patient data were utilized to calculate the mean difference in ISI and number of surgical procedures per year pre- and post-vaccination. Four studies reported individual data on ISI. Seven studies reported individual data on the number of surgical procedures per year. A total of 62 patients were analyzed with the primary outcome of ISI, and a total of 111 patients were analyzed with the primary outcome of the number of surgical procedures per year (Table II). Two unpublished data sets were provided by Chirila et al.[17] and Tjon Pian Gi et al.[3] and were included in the meta-analysis. The mean difference in ISI pre- and post-vaccination increased significantly across studies, and the mean difference in the number of procedures pre- and post-vaccination was negative in all included studies (Table III). Two studies reported on HPV sero-conversion, with HPV seropositivity of 100% (n = 27) prior to vaccination and 25.93% after vaccination (n = 7).

Heterogeneity was tested using the Higgens I^2 statistic. The heterogeneity of studies included in ISI was 94.67% ($p < 0.001$), and heterogeneity of studies included in the number of surgical procedures per year was 96.95% ($p < 0.001$). The contribution of each individual study to heterogeneity was analyzed, and Chirila et al. (study 1) was established as contributing most to heterogeneity. Thus, the mean difference in ISI and number of surgical procedures per year by random-effects meta-analysis was conducted both including and excluding study 1. There was a statistically significant increase in ISI and decrease in the number of surgical procedures per year after vaccination. Mean difference in ISI was 15.73 (95% CI, 1.46–29.99) (Fig. 2). Mean difference in surgical procedures per year was −4.43 (95% CI, −7.48 to −1.37) (Fig. 3). After excluding study 1, the mean difference in both ISI and number of surgical procedures per year remained significant. The mean difference in ISI pre- and post-vaccination was 9.26 (95% CI, 5.31–13.21), whereas the

mean difference in number of surgical procedures per year was −2.70 (95% CI, −4.23 to −1.18) (Figures S1 and S2). A meta-analysis of adult-only studies was also conducted. Three studies included data on number of surgical procedures per year in adult patients only- Yiu et al.[24] Matsuzaki et al.[21] and Goon et al.[20] Mean difference in surgical procedures per year pre- and post-vaccination in adult patients was −3.35 (95% CI, −5.87 to −0.83) (Fig. 4). ISI in adults was only available in Yiu et al.[24] and thus ISI adult-only meta analysis could not be conducted.

DISCUSSION

In this study, pooled data of patients with RRP showed that there was a statistically significant increase in ISI, as well as reduction in the number of procedures per year after HPV vaccination. The majority of patients were male, with HPV-6 associated adult-onset RRP. Research on HPV vaccination in the treatment of RRP has been limited to institutional studies, which are heterogenous, have small sample sizes, and may not hold external validity for larger populations. In addition, results of these studies have been mixed, with some showing no effect of HPV vaccination on RRP.[16,18,23,25–29] Other studies that have shown the efficacy of HPV vaccination as an adjuvant therapy have also been limited by small sample size.[2,3,30]

The pathophysiology of RRP remains poorly understood, but it has been theorized that RRP is a multi-gene disease that relies on viral-induced polarization of both the innate and adaptive immune system.[26–28] HPV protein E6 derivatives have been implicated in Th2-like differentiation, which contributes to poor immune response.[29] Immunotherapy, such as interferon therapy and bevacizumab, have been a cornerstone of RRP adjuvant therapies, and may be effective because of immune maladaptation to HPV infection. HPV vaccination may similarly rely on enhanced immune response to improve outcomes in patients with RRP. A humoral response to HPV-6 and HPV-11 has been shown to be either nonexistent or slow in patients with RRP and infection, but significantly increased after vaccination.[2,12] Our systematic review included 2 studies that reported on HPV sero-conversion, with HPV seropositivity of 100% prior to vaccination and 25.93% after vaccination.[15,23] Improved response to HPV infection may explain the efficacy of HPV vaccination in the treatment of RRP.

A prior systematic review and meta-analysis examined the use of HPV vaccine as an adjuvant therapy in RRP in 2019.[31] This prior study found that surgical procedures per month decreased, and ISI increased in RRP patients after vaccination. Our study aimed to include new data sets published since this study and increase statistical power by utilizing a larger sample size for the meta-analysis. Our study had similar findings: there was a statistically significant increase in ISI and decrease in the number of surgical procedures per year after HPV vaccination. These findings suggest that vaccination may be an effective adjuvant therapy in the treatment of RRP. As most patients with RRP require multiple surgical procedures to maintain an adequate airway while preserving voice, differences in intersurgical interval and number of surgical procedures are clinically significant.[32]

Studies from the systematic review were excluded in the meta-analysis if there was missing individual patient data. Of the studies excluded from the meta-analysis, two failed to show treatment response to HPV vaccination, and exclusion of these studies may have impacted our findings.[16,18] For example, Hermann et al. reported no significant change in ISI after vaccination. However, this study followed only nine patients.[18] Of the remaining studies excluded from the meta-analysis, Milner et al. compared patients before and after vaccination and found a significant increase in ISI and fewer procedures post-vaccination, but when comparing these patients to an unvaccinated cohort, they found no significant difference.[16] This may be due to a differing baseline disease burden between cohorts. Papaioannou et al. showed a significant increase in ISI and decreased operations per year after vaccination.[3] Mauz et al. observed recurrence in only 2 of 13 vaccinated patients at a mean follow-up time of 54 months, whereas all 11 unvaccinated patients developed a relapse.[22] Matsuzaki et al. illustrated a significant decrease in laryngeal disease burden and decreased tumor incidence rate after vaccination.[21]

A major limitation of this study was the significant heterogeneity among studies included in our analysis. One study was found to contribute most to heterogeneity, but was still included in the analysis due to the significant number of patients included.[17] Random-effects meta-analysis both including and excluding this study demonstrated a significant increase in ISI and decrease in number of surgical procedures per year. This suggests that, although this study may have contributed to heterogeneity, the findings still support HPV vaccination as an effective adjuvant therapy in the treatment of RRP. A potential contribution to the high heterogeneity was analysis including both adult and pediatric groups. However, we were able to conduct an adult-only meta-analysis of surgical procedures per year, which showed a significant decrease in number of surgeries after vaccination. We were unable to conduct an adult-only meta-analysis of ISI due to limited data. Another limitation is the use of retrospective data in the majority of the studies, which can introduce selection bias in the results. In addition, while trying to control for publication bias by conducting a wide search and following guidelines, the selective inclusion of only published, positively-biased data may be a limitation as well.

Future studies, including randomized clinical trials and larger cohort studies with long-term follow-up, are needed to further evaluate the relationship between HPV vaccination and RRP. Further investigation into disease response to HPV vaccination based on HPV subtype, age at vaccination, and other risk factor stratification may also elucidate differing efficacies in different patients. For example, studies have shown that HPV-11 behaves anatomically more aggressively than HPV-6, but there is limited information on this postulate.[33] Furthermore, younger patients with HPV-11 tend to have a worse clinical course than older patients.[2,33] Future studies that account for these factors may contribute to more individualized patient care.

This study supports the use of HPV vaccination as an adjuvant therapy in the treatment of RRP in children and adults, as it is associated with a fewer number of surgical procedures per year and increased time between surgeries after vaccination. This may have a significant benefit to patients with RRP by impacting quality of life, health care utilization, and outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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BIBLIOGRAPHY

1. Tasca RA, Clarke RW. Recurrent respiratory papillomatosis. Arch Dis Child. 2006;91(8):689–691. 10.1136/adc.2005.090514. [PubMed: 16861486]
2. Tjon Pian Gi RE, San Giorgi MR, Slagter-Menkema L, et al. Clinical course of recurrent respiratory papillomatosis: comparison between aggressiveness of human papillomavirus-6 and human papillomavirus-11. Head Neck. 2015;37(11):1625–1632. 10.1002/hed.23808. [PubMed: 24955561]
3. Papaioannou VA, Lux A, Voigt-Zimmermann S, Arens C. Treatment outcomes of recurrent respiratory papillomatosis: retrospective analysis of juvenile and adult cases. HNO. 2018. Behandlungsergebnisse bei rezidivierender respiratorischer Papillomatose: Retrospektive Analyse juveniler und adulter Falle;66:7–15. 10.1007/s00106-017-0378-0.
4. Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. Laryngoscope. 2008;118(7):1236–1247. 10.1097/MLG.0b013e31816a7135. [PubMed: 18496162]
5. Bishai D, Kashima H, Shah K. The cost of juvenile-onset recurrent respiratory papillomatosis. Arch Otolaryngol Head Neck Surg. 2000;126(8):935–939. 10.1001/archotol.126.8.935. [PubMed: 10922223]
6. Derkay CS, Bluher AE. Recurrent respiratory papillomatosis: update 2018. Curr Opin Otolaryngol Head Neck Surg. 2018;26(6):421–425. 10.1097/MOO.0000000000000490. [PubMed: 30300210]
7. Sullivan C, Curtis S, Mouzakes J. Therapeutic use of the HPV vaccine inrecurrent respiratory papillomatosis: a case report. Int J Pediatr Otorhinolaryngol. 2017;93:103–106. 10.1016/j.ijporl.2016.12.035. [PubMed: 28109479]
8. Meszner Z, Jankovics I, Nagy A, Gerlinger I, Katona G. Recurrent laryngeal papillomatosis with oesophageal involvement in a 2 year old boy: successful treatment with the quadrivalent human papillomatosis vaccine. Int J Pediatr Otorhinolaryngol. 2015;79(2):262–266. 10.1016/j.ijporl.2014.11.022. [PubMed: 25496821]
9. Baumanis MM, Elmaraghy CA. Intersurgical interval increased with use of quadrivalent human papillomavirus vaccine (Gardasil) in a pediatric patient with recurrent respiratory papillomatosis: a case report. Int J Pediatr Otorhinolaryngol. 2016;91:166–169. 10.1016/j.ijporl.2016.10.032. [PubMed: 27863633]
10. Nyirjesy S, Osmundson P, Matrka L. Spontaneous regression of recurrent respiratory papillomatosis with HPV vaccination: a case study. J Voice. 2020;36:587.e21–587.e25. 10.1016/j.jvoice.2020.08.013.
11. Cai Y, Merea VS, Lee AH, Su GH, Caruana SM. Nasopharyngeal papillomas treated with CO_2 laser and human papillomavirus vaccination. Laryngoscope. 2017;127(10):2279–2281. 10.1002/lary.26580. [PubMed: 28407312]
12. Buchinsky FJ, Ruszkay N, Valentino W, et al. In RRP, serologic response toHPV is frequently absent and slow to develop. PLoS One. 2020;15(3): e0230106. 10.1371/journal.pone.0230106.
13. Zhang CQ, Yi S, Liu XJ, Nan BY, Huang SY, Chen BB. Safety and immunogenicity of a nonadjuvant human papillomavirus type 6 virus-like particle vaccine in recurrent respiratory papillomatosis. J Voice. 2019;33(3):363–369. 10.1016/j.jvoice.2017.12.002. [PubMed: 30224308]
14. Young DL, Moore MM, Halstead LA. The use of the quadrivalent human papillomavirus vaccine (gardasil) as adjuvant therapy in the treatment of recurrent respiratory papilloma. J Voice. 2015;29(2):223–229. 10.1016/j.jvoice.2014.08.003. [PubMed: 25619468]

15. Hirai R, Makiyama K, Matsuzaki H, Oshima T. Gardasil vaccination for recurrent laryngeal papillomatosis in adult men second report: negative conversion of HPV in laryngeal secretions. J Voice. 2018;32(4):488–491. 10.1016/j.jvoice.2017.07.017. [PubMed: 28866231]
16. Milner TD, Harrison A, Montgomery J, MacGregor FB, Buchanan MA, MacKenzie K. A retrospective case-control analysis of the efficacy of Gardasil((R)) vaccination in 28 patients with recurrent respiratory papillomatosis of the larynx. Clin Otolaryngol. 2018;43(3):962–965. 10.1111/coa.13076. [PubMed: 29380936]
17. Chirila M, Bolboaca SD. Clinical efficiency of quadrivalent HPV (types 6/11/16/18) vaccine in patients with recurrent respiratory papillomatosis. Eur Arch Otorhinolaryngol. 2014;271(5):1135–1142. 10.1007/s00405-013-2755-y. [PubMed: 24121781]
18. Hermann JS, Weckx LY, Monteiro Nurmberger J, Santos Junior GF, Campos Pignatari AC, Nagata Pignatari SS. Effectiveness of the human papillomavirus (types 6, 11, 16, and 18) vaccine in the treatment of children with recurrent respiratory papillomatosis. Int J Pediatr Otorhinolaryngol. 2016;83:94–98. 10.1016/j.ijporl.2016.01.032. [PubMed: 26968061]
19. Hocevar-Boltezar I, Maticic M, Sereg-Bahar M, et al. Human papilloma virus vaccination in patients with an aggressive course of recurrent respiratory papillomatosis. Eur Arch Otorhinolaryngol. 2014;271(12):3255–3262. 10.1007/s00405-014-3143-y. [PubMed: 24964770]
20. Kin Cho Goon P, Scholtz LU, Sudhoff H. Recurrent respiratory papillomatosis (RRP)-time for a reckoning? Laryngoscope Investig Otolaryngol. 2017;2(4):184–186. 10.1002/lio2.80.
21. Matsuzaki H, Makiyama K, Hirai R, Suzuki H, Asai R, Oshima T. Multi-year effect of human papillomavirus vaccination on recurrent respiratory papillomatosis. Laryngoscope. 2020;130(2):442–447. 10.1002/lary.27993. [PubMed: 30963598]
22. Mauz PS, Schafer FA, Iftner T, Gonser P. HPV vaccination as preventive approach for recurrent respiratory papillomatosis - a 22-year retrospective clinical analysis. BMC Infect Dis. 2018;18(1):343. 10.1186/s12879-018-3260-0. [PubMed: 30041619]
23. Makiyama K, Hirai R, Matsuzaki H. Gardasil vaccination for recurrent laryngeal papillomatosis in adult men: first report: changes in HPV antibody titer. J Voice. 2017;31(1):104–106. 10.1016/j.jvoice.2016.01.008. [PubMed: 27068425]
24. Yiu Y, Fayson S, Smith H, Matrka L. Implementation of routine HPV vaccination in the management of recurrent respiratory papillomatosis. Ann Otol Rhinol Laryngol. 2019;128(4):309–315. 10.1177/0003489418821695. [PubMed: 30595025]
25. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA. 1999;282(11):1054–1060. 10.1001/jama.282.11.1054. [PubMed: 10493204]
26. Bonagura VR, Hatam LJ, Rosenthal DW, et al. Recurrent respiratory papillomatosis: a complex defect in immune responsiveness to human papillomavirus-6 and −11. APMIS. 2010;118(6–7):455–470. 10.1111/j.1600-0463.2010.02617.x. [PubMed: 20553528]
27. Bonagura VR, Vambutas A, DeVoti JA, et al. HLA alleles, IFN-gamma responses to HPV-11 E6, and disease severity in patients with recurrent respiratory papillomatosis. Hum Immunol. 2004;65(8):773–782. 10.1016/j.humimm.2004.05.014. [PubMed: 15336778]
28. DeVoti JA, Rosenthal DW, Wu R, Abramson AL, Steinberg BM, Bonagura VR. Immune dysregulation and tumor-associated gene changes in recurrent respiratory papillomatosis: a paired microarray analysis. Mol Med. 2008;14(9–10):608–617. 10.2119/2008-00060.DeVoti. [PubMed: 18607510]
29. Rosenthal DW, DeVoti JA, Steinberg BM, Abramson AL, Bonagura VR. T (H)2-like chemokine patterns correlate with disease severity in patients with recurrent respiratory papillomatosis. Mol Med. 2012;18:1338–1345. 10.2119/molmed.2012.00284. [PubMed: 23019074]
30. Forster G, Boltze C, Seidel J, Pawlita M, Muller A. Juvenile Larynxpapillomatose--Impfung mit dem polyvalenten Spaltimpfstoff Gardasil. Laryngorhinootologie. 2008;87(11):796–799. 10.1055/s-2008-1077527. [PubMed: 18759217]
31. Rosenberg T, Philipsen BB, Mehlum CS, et al. Therapeutic use of the human papillomavirus vaccine on recurrent respiratory papillomatosis: a systematic review and meta-analysis. J Infect Dis. 2019;219(7):1016–1025. 10.1093/infdis/jiy616. [PubMed: 30358875]

32. Ivancic R, Iqbal H, deSilva B, Pan Q, Matrka L. Current and future management of recurrent respiratory papillomatosis. Laryngoscope Investig Otolaryngol. 2018;3(1):22–34. 10.1002/lio2.132.

33. Bedard MC, de Alarcon A, Kou YF, et al. HPV strain predicts severity ofjuvenile-onset recurrent respiratory papillomatosis with implications for disease screening. Cancers (Basel). 2021;13(11). 10.3390/cancers13112556.

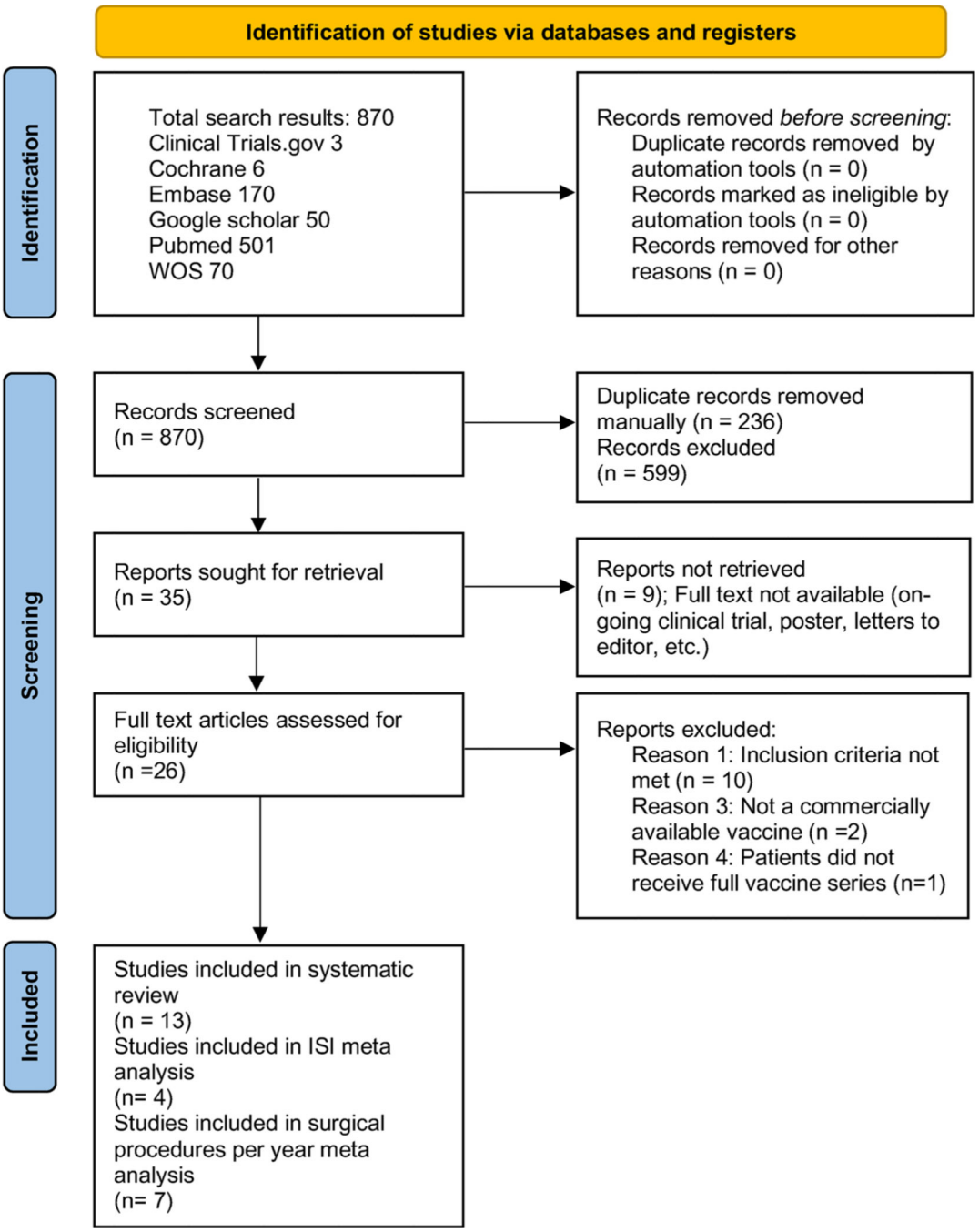

Fig. 1.

Flow chart detailing systematic review. Flow chart detailing identification of studies that met inclusion/exclusion criteria from databases and registers.

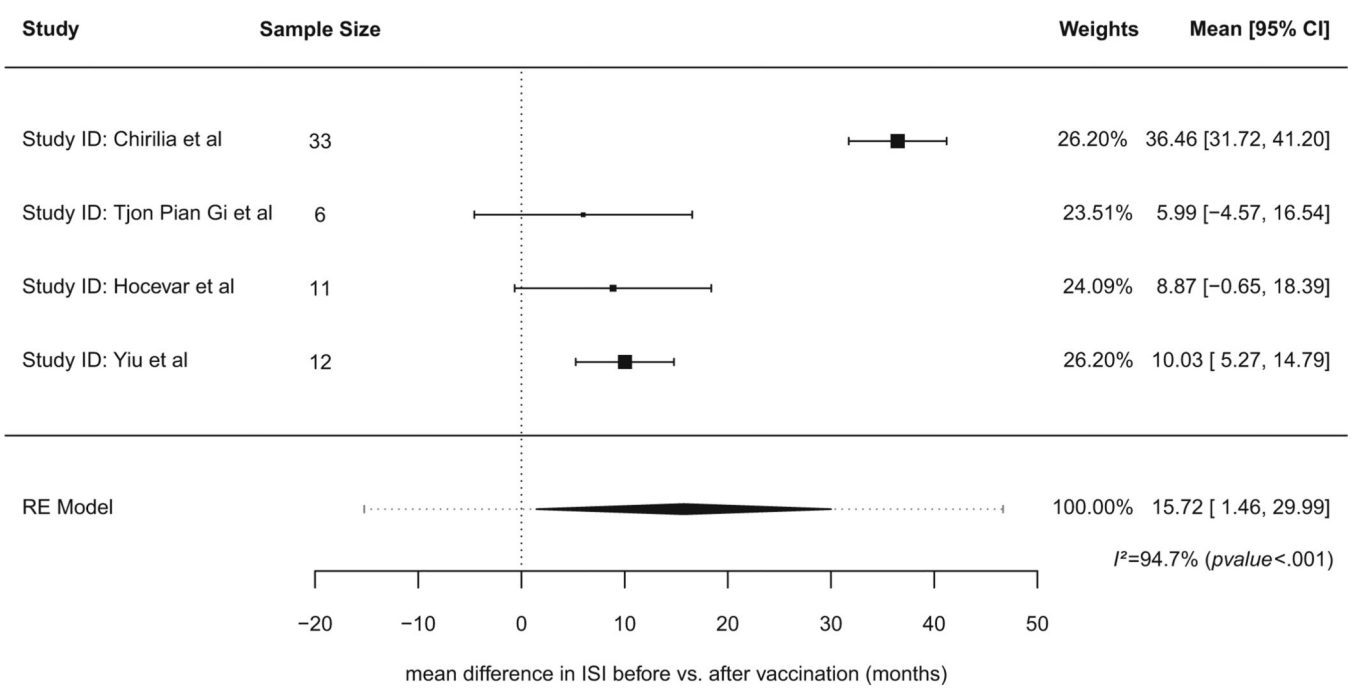

Fig. 2.

Random-effects meta-analysis of differences in intersurgical interval. The mean difference in ISI by random-effects meta-analysis was conducted. There was a statistically significant increase in ISI after vaccination. Mean difference in ISI was 15.73 months (95% CI, 1.46 to 29.99).

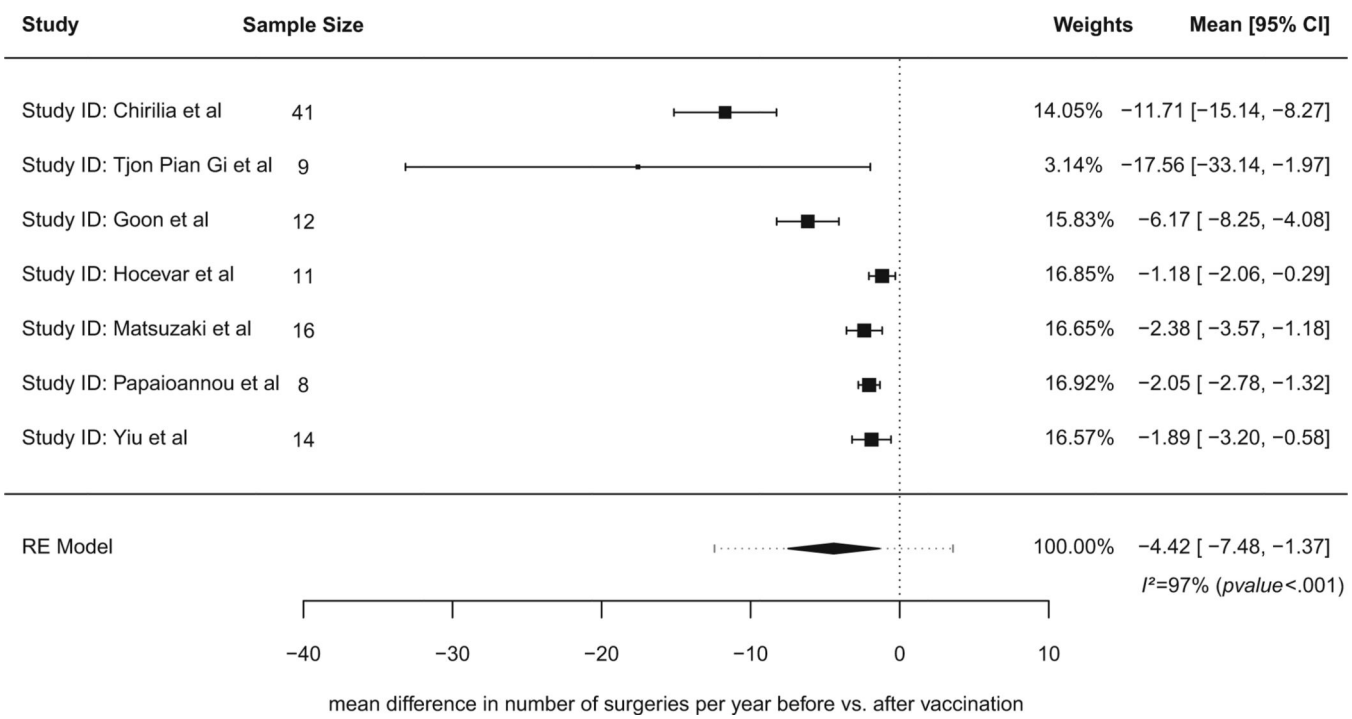

Fig. 3.

Random-effects meta-analysis of differences in number of procedures per year. The mean difference in number of surgical procedures per year by random-effects meta-analysis was conducted. There was a statistically significant decrease in the number of surgical procedures per year after vaccination. Mean difference in surgical procedures per year was −4.43 (95% CI, −7.48 to −1.37) (Figure 3).

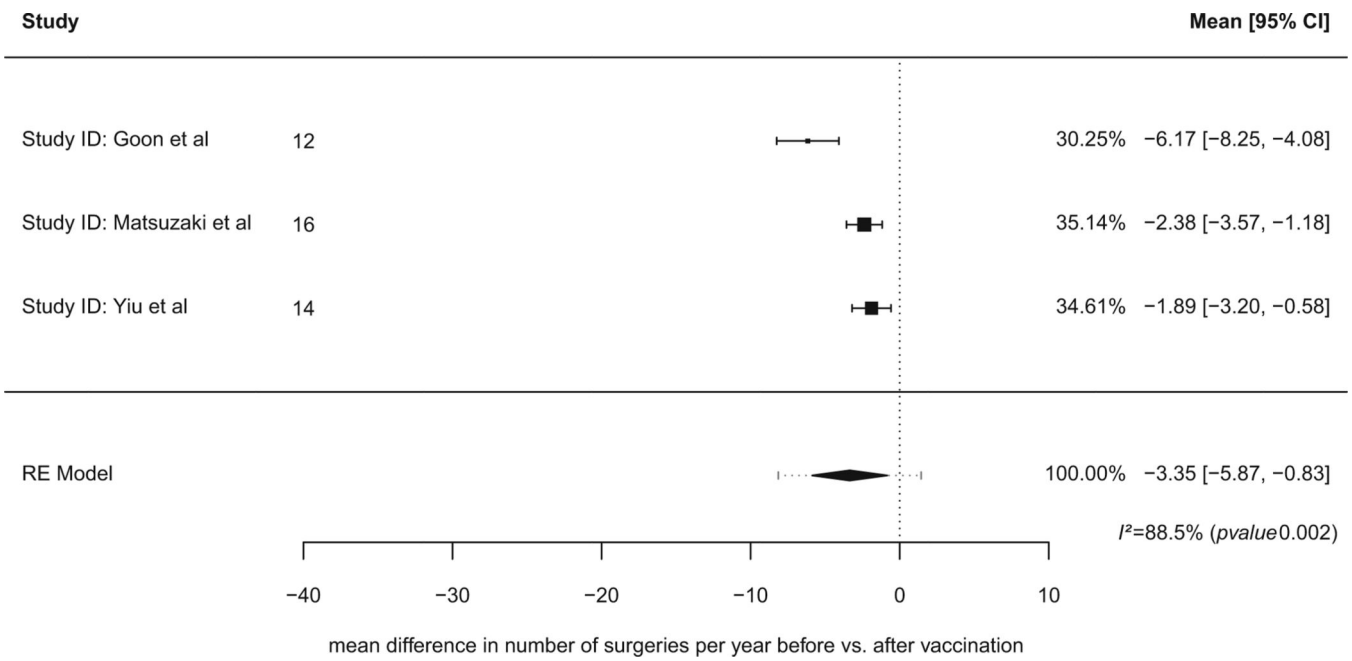

Fig. 4.

A meta-analysis of adult-only studies was conducted. Three studies included data on number of surgical procedures per year in adult patients only- Yiu et al, 2019, Matsuzaki et al, 2020, and Goon et al, 2017. There was a statistically significant decrease in number of surgical procedures per year pre- and post-vaccination in adult patients. The mean difference in surgical procedures per year in adult patients was −3.35 (95% CI, −5.87 to −0.83).

TABLE I.

Studies Included in Systematic Review.

	Study Design	Total number of patients	Number of patients who received vaccination	JoRRP/ AoRRP*	M/F	Adult/ Pediatric	Type of vaccine	Mean age at diagnosis	HPV 6/11	Number of patient with prior adjuvant therapy
Chirila et al.[17]	Case Series	13	13	4/9	9/4		Gardasil Quadrivalent	20.05	10/3	13
Tjon Pian Gi et al.[3]	Case Series	6	6	3/3	6/0		Gardasil Quadrivalent	16	5/1	5
Hermann et al.[18]	Case Series	9	9	9/0	6/3	0/9	Gardasil Quadrivalent	4.4	8/1	0
Hirai et al.[15]	Case Series	11	11		11/0	11/0	Gardasil Quadrivalent		10/1	
Hocevar-Boltezar et al.[19]	Case Series	11	11	4/7	5/6	10/1	Gardasil Quadrivalent	22.18	7/4	9
Kin Cho Goon et al.[20]	Cohort	12	12		8/4		Gardasil Quadrivalent			
Matsuzaki et al.[21]	Case Series	16	16	0/16	15/1	16/0	Gardasil Quadrivalent			
Mauz et al.[22]	Case Control	24	13	4/20	11/13		Gardasil Quadrivalent	40.79	11/5	
Makiyama et al.[23]	Case Series	12	12		12/0	12/0	Gardasil Quadrivalent		7/1	
Milner et al.[16]	Case Control	28	12		9/19		Gardasil Quadrivalent	36.4		
Papaioannou et al.[3]	Case Control	67	10				Gardasil Quadrivalent			
Yiu et al.[24]	Case Series	14	14		10/4		Gardasil Quadrivalent and 9-valent	(median: 46)		9
Young et al.[14]	Case Series	20	20		12/8		Gardasil Quadrivalent			15
Total		243	159	Total JoRRP: 24	Total Male: 125				Total HPV-6: 58	
				Total AoRRP: 55	Total Female: 48				Total HPV-11: 16	

N/A = not available.

*Definition of JoRRP and AoRRP differed between studies.

TABLE II.

Studies Included in Random-Effects Meta-Analysis.

	N	Complete ISI data	Complete data for No./year
Chirila et al.[17]	41	33	41
Tjon Pian Gi et al.[2]	9	6	9
Goon et al.[20]	12	0	12
Hocevar et al.[19]	11	11	11
Matsuzaki et al.[21]	16	0	16
Papaioannou et al.[3]	8	0	8
Yiu et al.[24]	14	12	14

* Chirila et al. and Tjon Pian Gi et al. contain published and unpublished data.

ISI = intersurgical interval; *N* = number of patients; No./yr = number of procedures per year.

TABLE III.

Data Per Study for Random-Effects Meta-Analysis.

	Pre-ISI, mean (SD), mo.	Post-ISI, mean (SD), mo.	Δ ISI, mean (95% CI), mo	Pre-No./yr, mean (SD)	Post-No./yr, mean (SD)	Δ No./year, mean (95% CI), yr	Avg. length of follow up, mo
Chirila et al.[17]*	3.78 (3.54)	40.24 (13.63)	36.46 (31.53–41.39)	12.61 (12.02)	0.90 (1.32)	−11.71 (8.16–15.25)	42.36
Tjon Pian Gi et al.[2]*	5.71 (5.37)	11.70 (14.26)	5.99 (−7.86–19.83)	19.33 (24.67)	1.78 (1.20)	−17.56 (−35.90–0.78)	23.56
Goon et al.[20]	-	-	-	6.42 (3.65)	0.25 (0.45)	−6.17 (−8.51 to −3.82)	37.25
Hocevar et al.[19]	9.04 (6.39)	17.91 (15.77)	8.87 (−1.96–19.70)	2.10 (1.12)	0.93 (0.63)	−1.18 (−2.18 to −0.17)	39.09
Matsuzaki et al.[21]	-	-	-	3.25 (1.88)	0.88 (1.31)	−2.38 (−3.68 to −1.07)	50.38
Papaiannou et al.[3]	-	-	-	2.39 (0.80)	0.35 (0.70)	−2.05 (−2.93 to −1.17)	29.00
Yiu et al.[24]	3.78 (3.42)	13.81 (8.01)	10.03 (4.68–15.37)	2.70 (2.53)	0.81 (0.86)	−1.89 (−3.33 to −0.45)	82.52

95% CI = 95% confidence interval; ISI = intersurgical interval; No./yr = number of procedures per year; SD, standard deviation.

*Chirila, et al and Tjon Pian Gi, et al contain published and unpublished data.