HPV vaccination after LEEP. A systematic review and meta-analysis.

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Abstract

Background: Prophylactic human papillomavirus (HPV) vaccines are highly effective in reducing premalignant lesions of the cervix. Recurrence is reported up to 17%. Little is known about the effect of HPV vaccines on women with CIN who already are HPV infected and CIN. Objective: Review of the literature addressing the question whether adjuvant vaccination with an HPV-vaccine in addition to LEEP treatment is effective in preventing recurrence of CIN-lesions. Search strategy: Medline search using Mesh terms. Selection criteria: Studies on HPV vaccination in addition to a LEEP procedure. One of the study parameters had to describe the effect of vaccination in addition to a surgical treatment. Data collection and Analysis: All results were assessed by two reviewers and meta-analysis performed. Main result: Six studies met the inclusion and exclusion criteria: one case report, three post-hoc analyses, one case-control study and one retrospective study. In the post-hoc analysis of three community-based clinical trials; the combined recurrence rate of CIN2+ was 1.49% (12/806) in the HPV- vaccinated group versus 3.51% (37/1052) in the non-HPV vaccinated group, with a combined RR of 0.41 (95% CI 0.21-0.78; P<0.01). The retrospective and the case-control study combined, reported an incidence of 2.07% (11/532) versus 6.92% (38/549) in favor for HPV vaccination, resulting in a significant positive vaccination effect in addition to LEEP treatment (RR 0.30 95%CI 0.16-0.58; P<0.01). Funding: None Keywords: HPV, CIN, VACCINACTION, LEEP

Tweetable abstract:

HPV vaccine after treatment shows reduced recurrence of CIN2+ 1.49% versus 3.51% and 2.07% versus 6.92% in favor for vaccination.

Introduction:

Cervical cancer and its precursor lesions are caused by a persistent infection with oncogenic types of human papillomavirus (hr-HPV)(1, 2). Worldwide, cervical cancer is diagnosed annually in more than 500,000 women(3, 4). Many studies have proven the efficacy and safety of a prophylactic HPV vaccine against the development of cervical intraepithelial neoplasia (CIN)(5). Therefore, cervical cancer (and other HPV-related diseases) are readily preventable with vaccinations.

About 80% of the HPV infections are cleared spontaneously by the body(6). It is not clear why this has not happened in women with a persistent HPV infection. These women are at risk for the development of CIN. Other premalignant conditions caused by a persistent HPV infection are vaginal, vulvar and anal dysplasia(7) and can also lead to cancer.

Different methods are available for the treatment of CIN. The most commonly used method is the Loop Electrosurgical Excision Procedure (LEEP). This procedure enables treatment and provides a reliable histologic interpretation(8). Nevertheless, treatment has been associated with side effects such as hemorrhage, infec-

tion, as well as with adverse pregnancy outcomes, such as premature rupture of membranes and premature birth. The risk of adverse pregnancy outcomes occur especially after multiple treatments(9-11).

Data on recurrent disease after treatment vary in the literature. Up to 17% of the women treated for cervical dysplasia can have residual or recurrent dysplasia(12) with repeated treatment as result. Especially adverse pregnancy outcomes are reasons for concern. Most women diagnosed with CIN are at reproductive age (25-40 years). Moreover, women treated for CIN have an increased risk of cervical vagina and vulvar cancer compared to women with normal primary smear test results(13, 14). Furthermore the cost efficiency of HPV vaccines is highly underestimated because adverse obstetrical outcomes, especially prematurity with neonatal morbidity and mortality, are not taken into account(15).

To avoid recurrent disease, the HPV infection should be prevented first. Different prophylactic HPV vaccines have been massively tested in big clinical trials. The vaccines are highly effectives against mainly HPV types 16 and 18. These clinical trials reported no clear therapeutic effect on patients with prior HPV exposure. Nonetheless, there is increasing evidence of an additional vaccine effect after treatment of clinical HPV related anogenital, dermal and oropharyngeal diseases(16-19). We performed a review of the literature with the aim of determining whether vaccination with an HPV vaccine in addition to LEEP treatment is effective in decreasing the recurrence of CIN.

Methods

With the aim to identify all publications in which a HPV vaccination was given in addition to the standard treatment for cervical dysplasia, we conducted an extensive search with a medical librarian of the literature from inception till 1th of august 2019 using the following databases: Pubmed, Medline and the Cochrane library. The search strategies contained various combinations of keywords and MeSH headings: Papillomavirus vaccines, HPV vaccine, human papilloma virus vaccination, Papillomaviridae, HPV, LEEP, conization, CIN, surgical therapy and biopsy. The search strategy is presented in appendix S1.

Eligible studies were human studies published in English or Dutch, without any restriction on study design. All articles that described the effect of vaccination in addition to a surgical treatment such as LEEP, conization, cone biopsy or other surgical therapy for cervical intra-epithelial neoplasia (CIN I-II-III) or high grade squamous intraepithelial lesion (HSIL) could be included. No limitation were made on age, number of sexual partners, HPV-type or prior treatment for HPV related diseases. Studies on HIV were excluded.

The titles and abstracts of all the citations retrieved by the searches were screened for relevance independently and separately by two of the authors (RL and WH). The full texts of the resulting articles were assessed on their relevance to this review. In case of disagreement, the third author (HB) assessed the relevance as well. The references of selected publications were checked on relevant other publications. The following details were sourced: Author, year of publication, age, study type, sample size, recurrence rate of cervical dysplasia after treatment and vaccination with a HPV vaccine. A random effect model is used to calculate the pooled effect size, anticipating heterogeneity between studies. Categorical data were summarized using the Mantel-Haenszel Risk Ratio (RR) with 95% confidence intervals (CI). Heterogeneity was calculated using the $\mathbf{I^2}$ statistic. Meta-analysis was performed using the software "Review Manager" version 5.3 from the Cochrane Collaboration.

Risk of bias was assessed using the modified Downs and Black (D&B) scale. The Downs and Black scale is also suitable for non-randomised trials (20). We used the checklist to score the reporting, the internal validity and external validity of the eligible studies. A High score indicates a better methodological quality. A score of 19 or higher indicates a high quality of the study as used in other studies (21). Whereas a score of <19 considered to be of low quality (See online supplementary table S2). The quality assessments of the included studies were used to categorize the level of evidence. We scored all studies below 19 and were subsequently methodologic of low quality.

Results

The search in the different databases, retrieved 1214 citations relating to our subject. After removing the

duplicates 930 were screened on titles or abstracts. We considered 39 studies possibly eligible and were retrieved for full text reading. Six studies were useful for our aim and these were included in this review (19, 22-26) (figure 1). Table 1 presents an overview of the selected studies. The characteristics of the studies are presented in Table S1 and the quality assessments are presented in supplementary S2.

Due to the heterogeneity we didn't perform a statistical pooling of the data of these five studies together. We conducted two different meta-analyses: one including the studies of Joura et al. Giannella et al. and Hildesheim et al, which are comparable in design and method, and one including the studies of Kang et al. and Ghelardi et al which are relatively comparable as well.

Giannella et al. described two different cases of a woman with a CIN lesion treated with LEEP. The first case involved a 33-year-old woman with a CIN 3, HPV 16 positive. At her own request she was given the quadrivalent HPV vaccine (HPV 6-11-16-18) after excision. At 6 months' follow-up, the PAP smear was normal, but the HPV 16 infection had persisted. At 18 months, CIN 3 was diagnosed with colposcopy, HPV 16 and 39 positive. The subsequent LEEP showed already an invasive carcinoma. The second case described a 35-year-old woman. At the first evaluation 6 months after LEEP, atypical squamous cells of undetermined significance were found while the HPV test was negative. The quadrivalent HPV vaccine was then administered. Twenty-four months after the conization, a CIN 3 was found with HPV type 33 positive.

The studies by Joura et al, Garland et al, and Hildesheim et al, all concern a sub analysis of a large community-based clinical trial for the evaluation of the effectivity and efficacy of HPV-vaccination in young women, irrespective of HPV state. The methods of these studies are similar. Joura et al. retrospectively analyzed data from a phase III study on the quadrivalent HPV vaccine (HPV type 6,11,16,18). Garland et al. and Hildesheim et al. analyzed data from phase III studies testing the efficacy of the bivalent vaccine (HPV type 16,18). In all three studies, routine follow-up and treatment were provided after vaccination (with HPV vaccine or hepatitis A/placebo vaccine as control, randomly assigned 1:1), if necessary, in accordance with local medical practice (table 2). The total recurrence of CIN2+ was 1.49% (12/806) in the HPV-vaccinated group versus 3.51% (37/1052) in the non-HPV vaccinated group. The combined RR was favorable for vaccination; i.e. 0.41 (95% CI 0.21-0.78; P<0,01) Figure 2.

Kang et al. retrospectively reviewed data from 737 women who had a LEEP for CIN lesions. Three hundred and sixty women had been vaccinated with the quadrivalent HPV vaccine; the other women had not been vaccinated at the time of treatment. Patient characteristics were similar between these two groups. The CIN lesion had recurred in 9 women in the vaccinated group (2.5%) versus 27 women (7.2%) in the non-vaccinated group, regardless of causal HPV-type. Regarding the vaccine- related HPV types (16 and 18) the CIN lesion had recurred in 5 women in the vaccinated group (2.5%) versus 18 women (8.5%) in the non-vaccinated group. Vaccination was an independent risk factor for recurrence (HR = 2.840; 95% CI, 1.335-6.042; P<0,01).

The latest, and only prospective, study published to date is the SPRERANZA project from Ghelardi et al. This prospective, non-randomized case-control study evaluated the post-treatment vaccination effect. Women aged 18-45 who were scheduled for cervical surgery for CIN2+ to [?] cervical cancer IA1, were counseled on HPV diseases and HPV vaccination in a 90-minutes session. After counseling, they were invited to participate in the trial, with the option to be vaccinated or not. The vaccination costs could not be reimbursed, but a discount was offered. Eventually, 536 women signed informed consent for participation, of which 248 women received the quadrivalent HPV vaccination. Baseline characteristics were similar between the group of vaccinated women and the group of non-vaccinated women. The median follow-up period was 36 months. Data of only 344 women were analyzed: almost 200 women had been lost to follow-up or had a follow-up period shorter than 6 months.

At 6 months, there was no statistically significant difference in HPV clearance between the groups (81.4% in the vaccinated group versus 84.9% in the non-vaccinated group). Clinical recurrence was found in 6.4% of the non-vaccinated group versus 1.2% of the vaccinated group (p=0.0112). The risk of CIN2+ after cervical surgical was significant reduced by 81.2% (95%CI, 34.3-95.7). In the vaccinated group, none of the CIN2+ lesions was related to HPV vaccine types (6-11-16-18).

The studies by Kang et al. and Ghelardi et al. are the only two known studies in which vaccination was given adjuvant to cervical surgery as a treatment for CIN2+. The recurrence rate of CIN2+ in these studies combined was favorable for HPV vaccination in addition to a LEEP: 2.07% (11/532) in vaccinated women versus 6.92% (38/549) in non-vaccinated women. Resulting in a significant positive vaccination effect in addition to a LEEP (RR 0.30 95%CI 0.16-0.58 P<0,01). (figure 3)

Discussion:

Why is adjuvant vaccination to cervical surgery an important issue? First, despite the availability of highly effective preventive vaccination, cervical dysplasia remains a massive problem worldwide, the HPV vaccination uptake in most countries is relatively low, estimated around 40% globally [28]. Secondly, most women are at reproductive age when diagnosed with cervical dysplasia. A relationship between cervical surgery and premature birth has been shown in many studies. The risk of premature birth is even higher after multiple treatments. Furthermore, the great emotional impact on the parents, the lifelong consequences in the prematurely born child with additional costs are considerably underestimated (15, 27).

The beneficial effect of prophylactic HPV vaccines for the primary prevention of HPV-related diseases has been confirmed by several studies (5). Still, the possible positive effect of adjuvant vaccination combined with surgical treatment has not been proven yet. Vaccination only in HPV-positive women with high grade cervical dysplasia did not reduce the incidence of cervical lesions (28). Nonetheless, there is increasing evidence that prophylactic HPV vaccinations in addition to usual treatment are of added value in the clinical manifestations of this virus. This holds not only for cervical premalignant lesions but also for other HPV-related clinical diseases.

The studies by Kang et al, and Ghelardi et al. both have their limitations regarding the methodology and outcome. In both studies, the women could decide for themselves whether to wanted be vaccinated, which may have resulted in selection bias. The study form Kang et al. concerned retrospective data and was primarily not designed to answer the question if adjuvant vaccination is beneficial. But despite the limitations, these studies show that vaccination is an independent risk factor for the recurrence of CIN2+ lesions. There is sufficient reason, there to further explore whether adjuvant vaccination is beneficial to prevent recurrence.

Joura et al. pooled data of 2 studies (FUTURE I and II); analysis revealed a significant decrease in the incidence of HPV-related diseases (cervical, vulvar and vaginal intraepithelial neoplasia and genital warts) when quadrivalent vaccination was given after LEEP treatment. This is a promising effect, which was only seen, irrespective of HPV type. The diseases related to the vaccine HPV-types, only the decrease in the occurrence of genital warts was significant. Although this study has some limitations, the authors concluded that vaccination has a positive effect to prevent recurrence possibly as a result of cross-protection. The subsequent abnormalities were predominantly low-grade abnormalities and occurred significantly less frequently with vaccination, especially after surgery. Like Joura et al. Garland et al., describe a promising 'secondary' benefit of vaccination for recurrent CIN2+ lesions, regardless of HPV-type. In contrast to Joura et al., however, they reported no reduction in the frequency of low-grade lesions but suggested a high chance for these lesions to regress spontaneously. The vaccine ought to protect against de novo HPV infection. The authors also suggest that the effect of cross-protection between different types of HPV may play a role. In addition, the effect relies on a possible boost of the immune response after vaccination.

Hildesheim et al., performed the same evaluation but found no evidence of viral clearance for the different HPV types and no difference in post-LEEP infections between the HPV types. Although they concluded that benefit of vaccination was not shown, both in results section and in the discussion section they refer to a significant vaccination effect to protect women for new HPV types. Furthermore they suggest possible selection bias. Characteristics of the two study groups were not similar at baseline and only 38% of the patients were HPV 16 or HPV 18 positive at baseline.

All three studies above mentioned studies were not designed nor intended to address the effect on the vaccination after LEEP and, in addition, were not powered for this aim. They included the same, young

population with a follow-up until 48 months for the primary study. The recurrence after LEEP (or other treatment) was evaluated after 60 days. The HPV is more easily cleared in younger patients than older patients. The follow-up period was very short with difficulty whether it is recurrence or residual disease. Furthermore, the vaccination was not administered during LEEP treatment period. In all three studies, the LEEP performed, if needed, in the follow-up period. Both Garland et al. and Joura et al. concluded that women who undergo surgical therapy after prior HPV vaccination have a lower risk of developing subsequent residual/recurrent CIN2+ compared to non-vaccinated women.

The two cases reported by Giannella et al. nicely illustrate the skepticism towards administration of the HPV vaccine after LEEP treatment. As case reports may cause bias, this report was not included in our meta-analysis.

For our meta-analysis we chose to have two separate analyses. The three post-hoc analyses are comparable in design and method, as well as the studies from Kang et al. and Ghelardi et al.

The discussion about a possible positive effect of adjuvant vaccination additional to regular treatment is still ongoing. Investigators in search of a vaccine against HPV noted an increased immune response with higher CD4+ and CD8+ T-cell activity after vaccination for severe dysplasia of the cervix (29, 30). This would imply that women in whom the HPV was not spontaneously cleared now have the antibodies from the vaccine. Another logical explanation for the positive adjuvant vaccination effect is the prevention of de novo HPV infections and re-infections.

Conclusion

This meta-analysis reveals to date only two studies have been published in which women received a HPV vaccination in addition to LEEP treatment for CIN2+ and evaluated the efficacy of HPV vaccination to prevent recurrence. Both studies had relatively small sizes and have their limitations. Nonetheless, in both studies a significant reduction in the recurrence of CIN2+ was seen with vaccination as an independent risk factor. The combined result of the sub-analysis of pooled data from large community-based trials was in favor of vaccination.

In conclusion the current literature does not provide a definite answer to the question whether adjuvant prophylactic HPV vaccination in addition to regular treatment has an additional effect. An RCT is lacking on this subject that may provide a definite answer to this issue. The ongoing VACCIN-trial (Dutch trial register: NL 7938) is expected to provide this answer.

Disclosure of interests:

This research was conducted in the absence of any commercial or financial relationships for all authors. Full disclosure of interests available to view online as supporting information.

Contribution to authorship:

All authors had access to all data and can take responsibility for the integrity and accuracy of the analysis. RL and HB designed the study. RL and WH developed the search strategy with assistance of a medical librarian. RL and WH acquired the data from all the studies. HB en RL performed the data-analysis. RL developed the first draft of the manuscript and HB en WH revised all manuscript drafts and approved the final version.

Details of ethical approval

Ethical approval was not required for this review. This study did not involve human or animal subjects, nor did it involve collecting data from patients' medical records.

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References

1. Munoz N, Castellsague X, de Gonzalez AB, Gissmann L. Chapter 1: HPV in the etiology of human cancer. Vaccine. 2006;24 Suppl 3:S3/1-10.

2. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet. 2007;370(9590):890-907.

3. Arbyn M, Castellsague X, de Sanjose S, Bruni L, Saraiya M, Bray F, et al. Worldwide burden of cervical cancer in 2008. Ann Oncol. 2011;22(12):2675-86.

4. Castellsague X. Natural history and epidemiology of HPV infection and cervical cancer. Gynecol Oncol. 2008;110(3 Suppl 2):S4-7.

5. Arbyn M, Xu L. Efficacy and safety of prophylactic HPV vaccines. A Cochrane review of randomized trials. Expert Rev Vaccines. 2018;17(12):1085-91.

6. Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. J Clin Virol. 2005;32 Suppl 1:S16-24.

7. Marty R, Roze S, Bresse X, Largeron N, Smith-Palmer J. Estimating the clinical benefits of vaccinating boys and girls against HPV-related diseases in Europe. BMC Cancer. 2013;13:10.

8. Martin-Hirsch PP, Paraskevaidis E, Bryant A, Dickinson HO. Surgery for cervical intraepithelial neoplasia. Cochrane Database Syst Rev. 2013(12):CD001318.

9. Kyrgiou M, Athanasiou A, Paraskevaidi M, Mitra A, Kalliala I, Martin-Hirsch P, et al. Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. BMJ. 2016;354:i3633.

10. Jin G, LanLan Z, Li C, Dan Z. Pregnancy outcome following loop electrosurgical excision procedure (LEEP) a systematic review and meta-analysis. Arch Gynecol Obstet. 2014;289(1):85-99.

11. Bjorge T, Skare GB, Bjorge L, Trope A, Lonnberg S. Adverse Pregnancy Outcomes After Treatment for Cervical Intraepithelial Neoplasia. Obstet Gynecol. 2016;128(6):1265-73.

12. van der Heijden E, Lopes AD, Bryant A, Bekkers R, Galaal K. Follow-up strategies after treatment (large loop excision of the transformation zone (LLETZ)) for cervical intraepithelial neoplasia (CIN): Impact of human papillomavirus (HPV) test. Cochrane Database Syst Rev. 2015;1:CD010757.

13. Strander B, Andersson-Ellstrom A, Milsom I, Sparen P. Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: population based cohort study. BMJ. 2007;335(7629):1077.

14. Ebisch RMF, Rutten DWE, IntHout J, Melchers WJG, Massuger L, Bulten J, et al. Long-Lasting Increased Risk of Human Papillomavirus-Related Carcinomas and Premalignancies After Cervical Intraepithelial Neoplasia Grade 3: A Population-Based Cohort Study. J Clin Oncol. 2017;35(22):2542-50.

15. Soergel P, Makowski L, Schippert C, Staboulidou I, Hille U, Hillemanns P. The cost efficiency of HPV vaccines is significantly underestimated due to omission of conisation-associated prematurity with neonatal mortality and morbidity. Hum Vaccin Immunother. 2012;8(2):243-51.

16. Pham CT, Juhasz M, Sung CT, Mesinkovska NA. The human papillomavirus vaccine as a treatment for human papillomavirus-related dysplastic and neoplastic conditions: A literature review. J Am Acad Dermatol. 2020;82(1):202-12.

17. Rosenberg T, Philipsen BB, Mehlum CS, Dyrvig AK, Wehberg S, Chirila M, 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):1016-25.

18. Dion GR, Teng S, Boyd LR, Northam A, Mason-Apps C, Vieira D, et al. Adjuvant Human Papillomavirus Vaccination for Secondary Prevention: A Systematic Review. JAMA Otolaryngol Head Neck Surg. 2017;143(6):614-22.

19. Kang WD, Choi HS, Kim SM. Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2-3)? Gynecol Oncol. 2013;130(2):264-8.

20. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377-84.

21. Samoocha D, Bruinvels DJ, Elbers NA, Anema JR, van der Beek AJ. Effectiveness of web-based interventions on patient empowerment: a systematic review and meta-analysis. J Med Internet Res. 2010;12(2):e23.

22. Giannella L, Mfuta K, Fodero C, Prandi S. Outcome of Nonpersonalized Human Papillomavirus Vaccinations During Postconization Follow-up: A Report of Two Cases. J Reprod Med. 2015;60(9-10):455-7.

23. Hildesheim A, Gonzalez P, Kreimer AR, Wacholder S, Schussler J, Rodriguez AC, et al. Impact of human papillomavirus (HPV) 16 and 18 vaccination on prevalent infections and rates of cervical lesions after excisional treatment. Am J Obstet Gynecol. 2016;215(2):212 e1- e15.

24. Garland SM, Paavonen J, Jaisamrarn U, Naud P, Salmeron J, Chow SN, et al. Prior human papillomavirus-16/18 AS04-adjuvanted vaccination prevents recurrent high grade cervical intraepithelial neoplasia after definitive surgical therapy: Post-hoc analysis from a randomized controlled trial. Int J Cancer. 2016;139(12):2812-26.

25. Joura EA, Garland SM, Paavonen J, Ferris DG, Perez G, Ault KA, et al. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: Retrospective pooled analysis of trial data. BMJ (Online). 2012;344(7851).

26. Ghelardi A, Parazzini F, Martella F, Pieralli A, Bay P, Tonetti A, et al. SPERANZA project: HPV vaccination after treatment for CIN2. Gynecol Oncol. 2018;151(2):229-34.

27. Van Hentenryck M, Noel JC, Simon P. Obstetric and neonatal outcome after surgical treatment of cervical dysplasia. Eur J Obstet Gynecol Reprod Biol. 2012;162(1):16-20.

28. Haupt RM, Wheeler CM, Brown DR, Garland SM, Ferris DG, Paavonen JA, et al. Impact of an HPV6/11/16/18 L1 virus-like particle vaccine on progression to cervical intraepithelial neoplasia in seropositive women with HPV16/18 infection. Int J Cancer. 2011;129(11):2632-42.

29. de Vos van Steenwijk PJ, Ramwadhdoebe TH, Lowik MJ, van der Minne CE, Berends-van der Meer DM, Fathers LM, et al. A placebo-controlled randomized HPV16 synthetic long-peptide vaccination study in women with high-grade cervical squamous intraepithelial lesions. Cancer Immunol Immunother. 2012;61(9):1485-92.

30. Roman LD, Wilczynski S, Muderspach LI, Burnett AF, O'Meara A, Brinkman JA, et al. A phase II study of Hsp-7 (SGN-00101) in women with high-grade cervical intraepithelial neoplasia. Gynecol Oncol. 2007;106(3):558-66.

Figure legends:

Table 1: Overview of articles

*Table 2: v/c = vaccine versus control, *treatment of any HPV related disease, ** CIN 2 of higher*

Figure 1: PRISMA Flow Diagram

Figure 2: Figure 2. Forest plot of the 3 sub analysis of recurrence of CIN2+ in women previously vaccinated that developed CIN 2-3 and subsequently received a LEEP.

Figure 3: Forest plot of the of recurrence of CIN2+ in women vaccinated adjuvant to cervical surgery as a treatment for CIN2+ lesions.

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Table 1 Overview of articles.docx available at https://authorea.com/users/300229/articles/429873-hpv-vaccination-after-leep-a-systematic-review-and-meta-analysis

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Table 2.vaccine versus control. docx.docx available at https://authorea.com/users/300229/articles/429873-hpv-vaccination-after-leep-a-systematic-review-and-meta-analysis

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