REVIEW

Should female sex workers be offered HPV vaccination?

Maarten F. Schim van der Loeff^{a,b,c}, Alex Vorsters^d, Elske Marra^a, Pierre Van Damme^d, and Arjan Hogewoning^{a,e}

^aDepartment of Infectious Disease, Public Health Service Amsterdam, Amsterdam, The Netherlands; ^bDepartment of Internal Medicine, Amsterdam Infection & Immunity Institute (AIII), Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands; ^cAmsterdam Public Health research institute, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands; ^dCentre for the Evaluation of Vaccination, Vaccine & Infectious Disease Institute, University of Antwerpen, Antwerp, Belgium; ^eDepartment of Dermatology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands

ABSTRACT

Prophylactic vaccines are efficacious in preventing Human Papillomavirus (HPV) infection and subsequent cervical intraepithelial neoplasia (CIN), cervical cancer, other anogenital cancers, and anogenital warts. Female sex workers (SW) are at increased risk of acquiring sexually transmitted infections, including HPV. There are several reasons to offer HPV vaccination to SW: they are at high risk for HPV and often unvaccinated, and the immunogenicity of the vaccine is also excellent in previously HPV exposed women. Furthermore, women with disease caused by HPV may still benefit from vaccination. The efficacy of vaccinating mid-adult women (26–44 years old) against persistent HPV infection and CIN2+ is good. Although an SW may have been infected or exposed to HPV, she may not have been exposed to all vaccine-included hrHPV types. Vaccination induces mucosal immunity via the production of neutralizing antibodies on the surface of the female genital tract, thus preventing potential transmission to clients.

Nevertheless, some considerations argue against offering vaccination to SWs. Current vaccines are only prophylactic and as such, do not affect current HPV infections. Women who have previously cleared HPV infections, may do so again and thus not need vaccination. Fewer SW might be naïve to HPV-types than currently thought. HPV vaccination has probably no effect on latent infections. Vaccinating sometime after sexual debut could be too late, as infections have already occurred.

Taken together, some data suggest that vaccination of SW may offer health benefits, also for the community, but sufficient evidence is lacking. In certain cases, HPV vaccination of SW may be recommended. Evidence-based, public health decisions concerning vaccination of SW are challenging and could be facilitated with more research in this high-risk group.

ARTICLE HISTORY

Received 21 December 2018

Revised 12 March 2019

Accepted 28 March 2019

KEYWORDS

Human Papillomavirus; sex worker; vaccine; effectiveness

Introduction

Since about 10 years, there are efficacious prophylactic vaccines able to prevent Human Papillomavirus (HPV) infection, thereby averting cervical intraepithelial neoplasia (CIN), the precursor of cervical cancer, and eventually cervical cancer.^{1–6} The vaccines also prevent other anogenital cancers caused by HPV, and two of the HPV vaccines protect against anogenital warts.

Female sex workers (SW) are known to be at increased risk for sexually transmitted infections, including HPV infection.^{7,8} Condoms offer only limited protection against HPV infection,^{9–12} presumably because HPV may infect mucosa and skin of the anogenital area, not just the glans penis or cervix. Condom use among SW varies between populations and settings (e.g., very high among SW in Amsterdam,^{12,13} but much lower in some other settings¹⁴). Female SW tend to be relatively young women, with almost half under 26 years of age.¹⁵ There are several strong arguments why HPV vaccination should be offered to SW.

Reasons to offer HPV vaccination to SW

First, SWs are indeed at high risk for HPV infection, the precursors of cervical cancer,^{7,15–19} and thus cervical cancer.

They are also at higher risk for anogenital warts and may be at higher risk for other anogenital cancers.

Second, women currently working as SW are unlikely to have been offered HPV vaccination in the past. This could have been due to [1] lack of HPV vaccination programs in their country of upbringing, [2] having an age outside the age range recommended for HPV vaccination, [3] access issues for the immunization program, or [4] opting out of vaccination. Many SW do not practice in their home country or region, but abroad. In high-income European countries SW often originate from Eastern European, Latin American or African countries,^{7,8,13} where many countries have not (yet) included HPV vaccination in their National Immunization Programmes.²⁰ It comes as no surprise then that many women currently working as SW in Europe or other high-income countries have not been vaccinated, which is expected to be even more so in low-income countries.

Third, immunogenicity of the vaccine is excellent in all women, including those previously exposed to HPV-types contained in the vaccine.^{21–23}

Fourth, women with disease caused by HPV may still benefit from vaccination. Recent studies have shown that the recurrence rate of disease after surgical treatment is lower among vaccinated women than among those non-vaccinated.^{24–26}

Fifth, several randomized control trials (RCT) have demonstrated the efficacy of vaccinating mid-adult women (26–44 years) against persistent HPV infection and CIN2+,^{21–23,27,28} which is important given that a substantial proportion of SW is aged 26 or higher. In one RCT vaccine efficacy in mid-adult women was less than that shown in RCTs of women aged 26 years or less, and efficacy was only shown in women not currently infected with the relevant HPV types. Nevertheless, analysis of data from the PATRICIA RCT showed that the vaccine was efficacious in preventing persistent infection and CIN1+ in women with serological evidence of previous HPV 16/18 infection.²⁹

Sixth, although many SW may previously or currently be infected with several HPV types, they might not have been exposed to or infected with all relevant hrHPV types. For example, we found HPV infection to be very common among SW in Amsterdam, the Netherlands, with 78% having at least one vaginal HPV infection. However, 64% were not currently infected with HPV-16 in the anus or cervix and were seronegative for HPV-16, suggesting that no previous HPV-16 infection had taken place. These percentages were even higher for the other hrHPV types.⁸ This means SW can still benefit from HPV vaccination; vaccination may not protect against types they are currently infected with, but will still offer protection against types they are currently not infected with.

Finally, another reason for vaccinating SW could be to reduce transmission. Vaccination is thought to induce mucosal immunity via vaccine-induced neutralizing antibodies on the surface of the female genital tract, thus preventing further spread and potential transmission to clients.³⁰ SW are core-transmitters of STI and vaccination could play an important role in limiting transmission to male clients and subsequently to other women. Stopping onward transmission from SW to their clients could have a downstream effect on reducing overall HPV burden in the population. For example, in Amsterdam, the Netherlands, around 5,000 female SW are working, and they have a mean of 660 sex contacts per SW per year (Unpublished data STI clinic, Amsterdam), suggesting about 3.3 million sex contacts per annum. Assuming that 40% of SW are infected with at least one high-risk HPV contained in the nine-valent vaccine,⁸ and further assuming a low per-sex act transmission risk of 20%, and 25% of clients already being infected with the HPV type concerned, then nearly 500,000 HPV transmissions could be prevented per year.

Reasons not to offer vaccination to SW

Notwithstanding these reasons, there are also some considerations arguing against offering vaccination.

The first problem is that currently available vaccines are prophylactic and as such, do not affect existing HPV infections.²⁹ Since SW have been highly exposed to HPV and may have persistent infections or CIN/AIN (anal intraepithelial neoplasia), vaccinating SW against HPV would have limited effectiveness. Although there are no data from RCTs on vaccine efficacy in SW, there is one trial on vaccination of presumably heavily pre-exposed

people, conducted by the AIDS Clinical Trials Group (protocol A5298). In this RCT, which included HIV-positive people, 82% of whom were men who have sex with men (MSM) and 18% women, no efficacy of the quadrivalent vaccine was demonstrated against persistent anal HPV infection compared to placebo.^{31,32} There are good reasons to assume that HIV infection or immunodeficiency *per se* do not strongly affect the immunogenicity and efficacy of HPV vaccines.^{33–35} Therefore, the underlying cause of non-protection by vaccination might have been due to a study population highly pre-exposed to HPV, similar to SW, rather than HIV-infection itself.

A second consideration is that women who have apparently cleared HPV infection of a given HPV type can be assumed to mount immune responses against subsequent infections of the same type, resulting in a cleared re-infection. In this instance, vaccination would not provide any additional effects to the host's natural immune response. There are no data to support or refute this hypothesis. However, Schiller³⁶ does point out that, unlike vaccination, natural infection does not induce strong neutralizing protection in previously infected women. This implies that transmission to sexual partners could occur prior to clearing re-infection in unvaccinated women, whereas transmission to others could be prevented by protection against re-infection in vaccinated women.

A third problem is the challenge of how to unambiguously ascertain a woman's HPV status. As in the Amsterdam data cited above,⁸ it appears, for a specific HPV type, that being HPV DNA negative would indicate no current infection and being seronegative would indicate no previous exposure. However, not all women seroconvert after infection with HPV.^{37,38} The actual number not currently or previously infected with a certain HPV type could be conceivably overestimated and thus the fraction of women possibly benefiting from vaccination could also be overestimated.

Fourth, related to the issue above, there is an ongoing debate around clearance versus latency.³⁹ In the literature, most studies infer clearance of an HPV type if that type was detected at one or more visits and is no longer detected at a subsequent visit(s). However, previously detected HPV types that are no longer detectable may have in fact entered into a latent stage. Various studies have suggested that latency is not a rare state.^{40,41} Latent HPV infections could later become reactivated, e.g., during menopause, after HIV seroconversion,^{42–44} or due to local inflammation. If this is indeed the case, then seemingly HPV-uninfected SW may harbor various latent HPV infections. Considering that the virus is intracellular and vaccine-induced antibodies cannot bind to virus involved in these established infections, HPV vaccination would probably have no effect on latent infections. Perhaps vaccination could protect against recrudescence of latent infections, but there are no data to support this claim.

Fifth, a recent study by Silverberg and colleagues⁴⁵ assessed the effectiveness of catch-up vaccination (vaccinating from age 14 years) using the quadrivalent vaccine against CIN2+ and CIN3+. They observed significant protection by vaccination among women offered catch-up

vaccination at ages 14–20 years, but there was no conferred protection against CIN2+ or CIN3+ when providing the first dose at age 21–26. This result suggests that vaccinating sometime after sexual debut could be too late, as infections have already occurred.

Discussion

There are several ways in which the impact of HPV vaccination of SW needs to be considered. Are we aiming for an impact on individual SW, on the population of SW, or on the general population?

The question raised in the title of this article is meant for public health services considering HPV prevention in SW. There are no clear-cut data about the effectiveness of HPV vaccination of highly, pre-exposed women, while indirect evidence suggests some degree of effectiveness. An evidence-based decision cannot, therefore, be made to include HPV vaccination as part of a health-care package aimed at SW.

This question could also be raised by public health services wanting to protect the community at large against HPV-induced disease. Because vaccination induces mucosal immunity, thereby making SW unable to further transmit HPV of vaccine-related types (even though their pre-existing HPV infections would not be cured), vaccinating SW could provide health benefits for the (male and female) population at large.

This question could also be raised by a clinician or health professional offering care and prevention to an SW. Not all SW are the same and in individual cases, the balance may favor vaccination. For example, many of the arguments above are under the assumption that women self-identifying as SW have been working in the sex industry for some time. These SWs may have already had scores of sex partners and thus have been exposed multiple times to many HPV types, and vaccination would not be warranted. However, if a woman in contact with health services indicates that she has recently started or plans to start sex work, has had few previous sex partners, or has had little or no vaginal or anal sex, then HPV vaccination should certainly be recommended, alongside other relevant health advice, such as condom use.

Finally, although not discussed above, one key advice to all women of reproductive age, especially SW, is to regularly attend a screening for cervical cancer, a proven way of preventing cervical cancer.⁴⁶

Clearly, much is still unclear, and studies are needed to clarify some of the issues. Key research questions to be addressed in a public health research setting would be the uptake of vaccination and the completion rate of vaccine doses. Conducting an RCT or observational study to assess the vaccine effectiveness in this group will be difficult, because of the required large sample size and the need for several years of follow-up in a group that is very mobile.

In conclusion, there are data suggesting that vaccination of SW offers some health benefits, also extending to the community, but strong evidence is lacking. Evidence-based public health decisions concerning vaccination of SW are therefore challenging and could be facilitated with more research in this

high-risk group. Research into uptake and completion of vaccination when offered is needed, as are long-term studies on the effectiveness of vaccination in highly pre-exposed women. In individual cases, HPV vaccination of SW may be recommended.

Acknowledgments

We thank Dr. Anders Boyd (GGD Amsterdam) for his feedback and advice on an earlier version of this manuscript.

Disclosure of potential conflicts of interest

The institution of MFSvdl received study funding from Sanofi Pasteur MSD and Janssen Infectious Diseases and Vaccines; he was a co-investigator in a Merck-funded investigator-initiated study; he was an investigator on a Sanofi Pasteur MSD sponsored trial; he served on a vaccine advisory board of GSK; his institution received in-kind contribution for an HPV study from Stichting Pathologie Onderzoek en Ontwikkeling (SPOO).

The institute of AV and PVD received unrestricted education grants from Sanofi Pasteur MSD, Merck, and GSK. AV and PVD participated in advisory board meetings of Merck.

The other authors have no conflicts of interest.

References

1. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med.* 2007 May 10;356(19):1915–27. PubMed PMID: 17494925.
2. Paavonen J, Jenkins D, Bosch FX, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter DL, Kitchener HC, Castellsague X, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. *Lancet.* 2007 Jun;369(9580):2161–70. Erratum in: *Lancet.* 2007 Oct 20;370(9596):1414. PubMed PMID: 17602732. doi:10.1016/S0140-6736(07)60946-5.
3. Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, Kitchener H, Castellsague X, Teixeira JC, Skinner SR, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet.* 2009;374(9686):301–14. PubMed PMID: 19586656.
4. Apter D, Wheeler CM, Paavonen J, Castellsagué X, Garland SM, Skinner SR, Naud P, Salmerón J, Chow SN, Kitchener HC, et al. Efficacy of human papillomavirus 16 and 18 (HPV-16/18) AS04-adjuvanted vaccine against cervical infection and precancer in young women: final event-driven analysis of the randomized, double-blind PATRICIA trial. *Clin Vaccine Immunol.* 2015 Apr;22(4):361–73. Epub 2015 Feb 4. PubMed PMID: 25651922; PubMed Central PMCID: PMC4375348. doi:10.1128/CVI.00591-14.
5. Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, Moreira ED Jr, Ngan Y, Petersen LK, Lazcano-Ponce E, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med.* 2015 Feb;372(8):711–23. PubMed PMID: 25693011. doi:10.1056/NEJMoa1405044.
6. Huh WK, Joura EA, Giuliano AR, Iversen OE, de Andrade RP, Ault KA, Bartholomew D, Cestero RM, Fedrizzi EN, Hirschberg AL, et al. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16–26 years: a randomised, double-blind trial. *Lancet.* 2017 Nov 11;390(10108):2143–59. Epub 2017 Sep 5. PubMed PMID: 28886907. doi:10.1016/S0140-6736(17)31821-4.

7. Vorsters A, Cornelissen T, Leuridan E, Bogers J, Vanden Broeck D, Benoy I, Goossens H, Hens N, Van Damme P. Prevalence of high-risk human papillomavirus and abnormal pap smears in female sex workers compared to the general population in Antwerp, Belgium. *BMC Public Health*. 2016 Jun 7;16:477. PubMed PMID: 27266509; PubMed Central PMCID: PMC4897854. doi:10.1186/s12889-016-3099-5.
8. Marra E, Kroone N, Freriks E, van Dam CL, Alberts CJ, Hogewoning AA, Bruisten S, van Dijk A, Kroone MM, Waterboer T, et al. Vaginal and anal human papillomavirus infection and seropositivity among female sex workers in Amsterdam, the Netherlands: prevalence, concordance and risk factors. *J Infect*. 2018 Apr;76(4):393–405. Epub 2017 Dec 28. PubMed PMID: 29289562. doi:10.1016/j.jinf.2017.12.011.
9. Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sex Transm Dis*. 2002 Nov;29(11):725–35. PubMed PMID: 12438912.
10. Winer RL, Hughes JP, Feng Q, O'Reilly S, Kiviat NB, Holmes KK, Koutsky LA. Condom use and the risk of genital human papillomavirus infection in young women. *N Engl J Med*. 2006 Jun 22;354(25):2645–54. PubMed PMID: 16790697.
11. Pierce Campbell CM, Lin HY, Fulp W, Papenfuss MR, Salmerón JJ, Quiterio MM, Lazcano-Ponce E, Villa LL, Giuliano AR. Consistent condom use reduces the genital human papillomavirus burden among high-risk men: the HPV infection in men study. *J Infect Dis*. 2013 Aug 1;208(3):373–84. Epub 2013 May 3. PubMed PMID: 23644283; PubMed Central PMCID: PMC3699010. doi:10.1093/infdis/jit191.
12. Lam JU, Rebolj M, Dugué PA, Bonde J, von Euler-Chelpin M, Lyngé E. Condom use in prevention of Human Papillomavirus infections and cervical neoplasia: systematic review of longitudinal studies. *J Med Screen*. 2014 Mar;21(1):38–50. Epub 2014 Jan 31. Review. PubMed PMID: 24488594. doi:10.1177/09691413134522454.
13. van Dulm E, Marra E, Kroone MM, van Dijk AE, Hogewoning AA, Schim van der Loeff MF. Sexually transmitted infections among female sex workers in Amsterdam between 2011 and 2016: does risk vary by work location? *BMC Public Health*, In Press.
14. Okafor UO, Crutzen R, Aduak Y, Adebajo S, Van Den Borne HW. Behavioural interventions promoting condom use among female sex workers in sub-Saharan Africa: a systematic review. *Afr J AIDS Res*. 2017 Sep;16(3):257–68. Review. PubMed PMID: 28978291. doi:10.2989/16085906.2017.1358753.
15. Soohoo M, Blas M, Byraiah G, Carcamo C, Brown B. Cervical HPV infection in female sex workers: a global perspective. *Open AIDS J*. 2013 Dec 30;7:58–66. eCollection 2013. PubMed PMID: 24511334; PubMed Central PMCID: PMC3915319. doi:10.2174/1874613601307010058.
16. Mak R, Van Renterghem L, Cuvelier C. Cervical smears and human papillomavirus typing in sex workers. *Sex Transm Infect*. 2004 Apr;80(2):118–20. PubMed PMID: 15054172; PubMed Central PMCID: PMC1744807.
17. Shikova E, Todorova I, Ganchev G, Kouseva-Dragneva V, Kalascheva-Zaimova P. Prevalence of human papillomavirus infection among female sex workers in Bulgaria. *Int J STD AIDS*. 2011 May;22(5):278–80. PubMed PMID: 21571976. doi:10.1258/ijsa.2009.009362.
18. Peng RR, Li HM, Chang H, Li JH, Wang AL, Chen XS. Prevalence and genotype distribution of cervical human papillomavirus infection among female sex workers in Asia: a systematic literature review and meta-analysis. *Sex Health*. 2012 May;9(2):113–19. Review. PubMed PMID: 22498154. doi:10.1071/SH11066.
19. Leung KM, Yeoh GP, Cheung HN, Fong FY, Chan KW. Prevalence of abnormal Papanicolaou smears in female sex workers in Hong Kong. *Hong Kong Med J*. 2013 Jun;19(3):203–06. Epub 2013 May 6. PubMed PMID: 23650200. doi:10.12809/hkmj133917.
20. Gallagher KE, LaMontagne DS, Watson-Jones D. Status of HPV vaccine introduction and barriers to country uptake. *Vaccine*. 2018 Aug 6;36(32 Pt A):4761–67. Epub 2018 Mar 23. PubMed PMID: 29580641. doi:10.1016/j.vaccine.2018.02.003.
21. Castellsague X, Munoz N, Pitisuttithum P, Ferris D, Monsonego J, Ault K, Luna J, Myers E, Mallary S, Bautista OM, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24–45 years of age. *Br J Cancer*. 2011;105(1):28–37. PubMed PMID: 21629249. PubMed Central.
22. Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazcano-Ponce E, Salmerón J, Del Rosario-Raymundo MR, Verheijen RH, Quek SC, Da Silva DP, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. *Lancet*. 2014 Dec;384(9961):2213–27. Epub 2014 Sep 1. PubMed PMID: 25189358. doi:10.1016/S0140-6736(14)60920-X.
23. Wheeler CM, Skinner SR, Del Rosario-Raymundo MR, Garland SM, Chatterjee A, Lazcano-Ponce E, Salmerón J, McNeil S, Stapleton JT, Bouchard C, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. *Lancet Infect Dis*. 2016;16(10):1154–68. PubMed PMID: 27373900.
24. Joura EA, Garland SM, Paavonen J, Ferris DG, Perez G, Ault KA, Huh WK, Sings HL, James MK, Haupt RM, FUTURE I and II Study Group. 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*. 2012 Mar;344:e1401. PubMed PMID: 22454089; PubMed Central PMCID: PMC3314184. doi:10.1136/bmj.e1401.
25. 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 Aug;130(2):264–68. Epub 2013 Apr 26. PubMed PMID: 23623831. doi:10.1016/j.ygyno.2013.04.050.
26. Ghelardi A, Parazzini F, Martella F, Pieralli A, Bay P, Tonetti A, Svelato A, Bertacca G, Lombardi S, Joura EA. SPERANZA project: HPV vaccination after treatment for CIN2. *Gynecol Oncol*. 2018 Nov;151(2):229–34. Epub 2018 Sep 6. PubMed PMID: 30197061. doi:10.1016/j.ygyno.2018.08.033.
27. Muñoz N, Manalastas R Jr, Pitisuttithum P, Tresukosol D, Monsonego J, Ault K, Clavel C, Luna J, Myers E, Hood S, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24–45 years: a randomised, double-blind trial. *Lancet*. 2009 Jun 6;373(9679):1949–57. Epub 2009 Jun 1. PubMed PMID: 19493565. doi:10.1016/S0140-6736(09)60691-7.
28. Arbyn M, Xu L, Simoes C, Martin-Hirsch PPL. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. *Cochrane Database Syst Rev*. 2018;(5). Art. No.: CD009069. doi:10.1002/14651858.CD009069.pub3.
29. Szarewski A, Poppe WA, Skinner SR, Wheeler CM, Paavonen J, Naud P, Salmerón J, Chow SN, Apter D, Kitchener H, et al. Efficacy of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in women aged 15–25 years with and without serological evidence of previous exposure to HPV-16/18. *Int J Cancer*. 2012 Jul;131(1):106–16. Epub 2011 Oct 23. PubMed PMID: 21858807. doi:10.1002/ijc.26362.
30. Schiller JT, Davies P. Delivering on the promise: HPV vaccines and cervical cancer. *Nat Rev Microbiol*. 2004 Apr;2(4):343–47. Review. PubMed PMID: 15031733.
31. Cranston RD, Cespedes MS, Paczuski P, Yang M, Coombs RW, Dragavon J, Saah A, Godfrey C, Webster-Cyriaque JY, Chiao EY, et al. High baseline anal human papillomavirus and abnormal anal cytology in a phase 3 trial of the quadrivalent human papillomavirus vaccine in human immunodeficiency virus-infected individuals older than 26 years: ACTG 5298. *Sex Transm Dis*. 2018 Apr;45(4):266–71. PubMed

- PMID: 29528986; PubMed Central PMCID: PMC5868482. doi:[10.1097/OLQ.0000000000000745](https://doi.org/10.1097/OLQ.0000000000000745).
32. Wilkin TJ, Chen H, Cespedes MS, Leon-Cruz JT, Godfrey C, Chiao EY, Bastow B, Webster-Cyriaque J, Feng Q, Dragavon J, et al. A randomized, placebo-controlled trial of the quadrivalent human papillomavirus vaccine in human immunodeficiency virus-infected adults aged 27 years or older: AIDS clinical trials group protocol A5298. *Clin Infect Dis*. 2018 Oct 15;67(9):1339–46. PubMed PMID: 29659751; PubMed Central PMCID: PMC6186857. doi:[10.1093/cid/ciy274](https://doi.org/10.1093/cid/ciy274).
 33. Wilkin T, Lee JY, Lensing SY, Stier EA, Goldstone SE, Berry JM, Jay N, Aboulafia D, Cohn DL, Einstein MH, et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. *J Infect Dis*. 2010 Oct 15;202(8):1246–53. PubMed PMID: 20812850; PubMed Central PMCID: PMC3118428. doi:[10.1086/656320](https://doi.org/10.1086/656320).
 34. Heijstek MW, Scherpenisse M, Groot N, Tacke C, Schepp RM, Buisman AM, Berbers GA, van der Klis FR, Wulffraat NM. Immunogenicity and safety of the bivalent HPV vaccine in female patients with juvenile idiopathic arthritis: a prospective controlled observational cohort study. *Ann Rheum Dis*. 2014 Aug;73(8):1500–07. Epub 2013 May 30. PubMed PMID: 23723319. doi:[10.1136/annrheumdis-2013-203429](https://doi.org/10.1136/annrheumdis-2013-203429).
 35. Kojic EM, Kang M, Cespedes MS, Umbleja T, Godfrey C, Allen RT, Firnhaber C, Grinsztejn B, Palefsky JM, Webster-Cyriaque JY, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. *Clin Infect Dis*. 2014 Jul 1;59(1):127–35. Epub 2014 Apr 9. PubMed PMID: 24723284; PubMed Central PMCID: PMC4305143. doi:[10.1093/cid/ciu238](https://doi.org/10.1093/cid/ciu238).
 36. Schiller JT. The potential benefits of HPV vaccination in previously infected women. *EBioMedicine*. 2016 Aug;10:5–6. Epub 2016 Aug 3. PubMed PMID: 27515688; PubMed Central PMCID: PMC5006803. doi:[10.1016/j.ebiom.2016.08.005](https://doi.org/10.1016/j.ebiom.2016.08.005).
 37. Carter JJ, Koutsky LA, Wipf GC, Christensen ND, Lee SK, Kuypers J, Kiviat N, Galloway DA. The natural history of human papillomavirus type 16 capsid antibodies among a cohort of university women. *J Infect Dis*. 1996 Nov;174(5):927–36. PubMed PMID: 8896492.
 38. Edelstein ZR, Carter JJ, Garg R, Winer RL, Feng Q, Galloway DA, Koutsky LA. Serum antibody response following genital {alpha}9 human papillomavirus infection in young men. *J Infect Dis*. 2011 Jul 15;204(2):209–16. PubMed PMID: 21673030; PubMed Central PMCID: PMC3114468. doi:[10.1093/infdis/jir242](https://doi.org/10.1093/infdis/jir242).
 39. Gravitt PE. The known unknowns of HPV natural history. *J Clin Invest*. 2011 Dec;121(12):4593–99. Epub 2011 Dec 1. Review. PubMed PMID: 22133884; PubMed Central PMCID: PMC3225991. doi:[10.1172/JCI57149](https://doi.org/10.1172/JCI57149).
 40. Shew ML, Ermel AC, Tong Y, Tu W, Qadadri B, Brown DR. Episodic detection of human papillomavirus within a longitudinal cohort of young women. *J Med Virol*. 2015 Dec;87(12):2122–29. Epub 2015 Jun 25. PubMed PMID: 26112742. doi:[10.1002/jmv.24284](https://doi.org/10.1002/jmv.24284).
 41. Twisk DE, van der Sande MAB, van Eeden A, Heideman DAM, van der Klis FRM, de Vries HJC, Schim van der Loeff MF. Detection of incident anal high-risk human papillomavirus DNA in men who have sex with men: incidence or reactivation? *J Infect Dis*. 2018 Aug 24;218(7):1018–26. PubMed PMID: 29771378. doi:[10.1093/infdis/jiy276](https://doi.org/10.1093/infdis/jiy276).
 42. Strickler HD, Burk RD, Fazzari M, Anastos K, Minkoff H, Massad LS, Hall C, Bacon M, Levine AM, Watts DH, et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. *J Natl Cancer Inst*. 2005 Apr 20;97(8):577–86. PubMed PMID: 15840880.
 43. Wang C, Wright TC, Denny L, Kuhn L. Rapid rise in detection of human papillomavirus (HPV) infection soon after incident HIV infection among South African women. *J Infect Dis*. 2011;203:479–86.
 44. Nowak RG, Gravitt PE, Morrison CS, Gange SJ, Kwok C, Oliver AE, Howard R, Van der Pol B, Salata RA, Padian NS, et al. Increases in human papillomavirus detection during early HIV infection among women in Zimbabwe. *J Infect Dis*. 2011;203:1182–91.
 45. Silverberg MJ, Leyden WA, Lam JO, Gregorich SE, Huchko MJ, Kulasingam S, Kuppermann M, Smith-McCune KK, Sawaya GF. Effectiveness of catch-up human papillomavirus vaccination on incident cervical neoplasia in a US health-care setting: a population-based case-control study. *Lancet Child Adolesc Health*. 2018 Oct;2(10):707–14. Epub 2018 Aug 8. PubMed PMID: 30236379; PubMed Central PMCID: PMC6152835. doi:[10.1016/S2352-4642\(18\)30220-7](https://doi.org/10.1016/S2352-4642(18)30220-7).
 46. Vesco KK, Whitlock EP, Eder M, Lin J, Burda BU, Senger CA, Holmes RS, Fu R, Zuber S. Screening for cervical cancer: a systematic evidence review for the U.S. preventive services task force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011 May. PMID: 22132428. <http://www.ncbi.nlm.nih.gov/books/NBK66099/PubMed>