

RESEARCH PAPER

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Tempest in a teapot: A systematic review of HPV vaccination and risk compensation research

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ABSTRACT

There has been some concern among parents and in the media that vaccinating children against human papillomavirus could be seen as giving children permission to engage in risky sexual behaviors (also known as sexual disinhibition). Several studies have found this concern to be unfounded but there have been no attempts to synthesize the relevant studies in order to assess if there is evidence of sexual disinhibition. The aim of this study was to synthesize recent literature examining sexual behaviors and biological outcomes (e.g., sexually transmitted infections) post-HPV vaccination. We reviewed literature from January 1, 2008–June 30, 2015 using PubMed, CINAHL, and Embase with the following search terms: [(sex behavior OR sex behavior OR sexual) AND (human papillomavirus OR HPV) AND (vaccines OR vaccine OR vaccination)] followed by a cited reference search. We included studies that examined biological outcomes and reported behaviors post-vaccination in both males and females. Studies were reviewed by title and abstract and relevant studies were examined as full-text articles. We identified 2,503 articles and 20 were eventually included in the review. None of the studies of sexual behaviors and/or biological outcomes found evidence of riskier behaviors or higher rates of STIs after HPV vaccination. Instead, the studies found that vaccinated compared to unvaccinated individuals were less likely to report vaginal intercourse without a condom (OR = 0.5; 95%CI = 0.4–0.6) and non-use of contraception (OR = 0.27; 95%CI = 0.15–0.48) and unvaccinated participants had higher rates of Chlamydia (OR = 2.3; 95%CI = 1.06–5.00). These results should be reassuring to parents and health care providers.

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Introduction

In 2015, the Centers for Disease Control and Prevention (CDC) reported that there are approximately 79 million Americans who are currently infected with Human Papillomavirus (HPV) and 14 million new infections occur every year, making it the most common sexually transmitted infection (STI).¹ It is estimated that the worldwide prevalence of HPV infection in women without cervical abnormalities is 11–12%. This varies by region with higher rates in sub-Saharan Africa (24%), Eastern Europe (21%) and Latin America (16%).² Infection with HPV is a risk factor for serious health issues including genital warts, cervical cancer, anal cancer, penile cancer, oropharyngeal cancers, and recurrent respiratory papillomatosis.¹ Currently, there are 3 different HPV vaccines: 1) A bivalent vaccine (2vHPV) that protects against HPV types 16 and 18, 2 types that are responsible for about 70% of cervical cancer diagnoses;³ 2) A quadrivalent vaccine (4vHPV) that protects against HPV-16 and 18 as well as HPV-6 and 11, 2 types that cause about 90% of the cases of genital warts;⁴ and 3) A nine-valent HPV vaccine (9vHPV) was recently licensed by the US Food and Drug Administration, and protects against the 4 HPV

types in 4vHPV as well as 5 additional oncogenic types (HPV types 31, 33, 45, 52, and 58). 9vHPV has the potential to prevent 80–90% of cervical cancers, and many vulvar, vaginal, and anal cancers in addition to 90% of genital warts.⁵

Despite the recommendations made by national immunization advisory committees around the world, HPV vaccination rates, especially in the United States, remain suboptimal.^{6,7} For example, only 60.0% of adolescent girls and 41.7% of adolescent boys between the ages of 13 and 17 received one or more doses in the HPV vaccine series in the United States in 2014.⁸ These rates are even lower when examining the percentages of adolescents who have completed the series, which is necessary in order to receive the maximum protection from the vaccine.⁹ Several barriers to HPV vaccination exist including cost of the vaccination, lack of knowledge about HPV transmission, and parental concerns about vaccinating their children against an STI.¹⁰

One concern among parents, clinicians, and public health officials, which has received particular attention in the media, is that the introduction of the HPV vaccine will lead to risk compensation, a concept introduced by Wilde in the 1980s that

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he called Risk Homeostasis Theory (RHT).¹¹ RHT suggests that individuals have innate set points for risk tolerance and that they change their behaviors based on perceived risk in order to maintain their set point. According to RHT, then, if an individual believes that a measure protects him/her from a certain risk, then he/she would be more likely to engage in risky behaviors.¹¹ Critics of the HPV vaccine have expressed concern that the receipt of the vaccine could cause adolescents to engage in riskier sexual behavior due to perceived protection from sexually transmitted infections.¹² This is a concern that has arisen throughout the world. For example, several Roman Catholic bishops in Canada discouraged vaccination, stating that school-based vaccination “sends a message that early sexual intercourse is allowed”¹³ and that abstinence is the “only truly healthy choice.”^{14,15} One study using qualitative interviews of mothers in the United Kingdom found it described as giving girls a “carte blanche” to engage in behaviors that put them at risk for pregnancy, HIV, and STIs.¹⁶

These parental concerns might have been influenced by stories they encountered in the media.¹⁷⁻¹⁹ A US study found a majority of news articles about HPV vaccination were neutrally toned but the results also indicated that there were several important informational facts that were omitted in the articles, namely information about side effects, duration of protection, and information about catch-up vaccination.²⁰ Internet use and accuracy of internet information regarding the HPV vaccine are important considerations because some studies have found that vaccine concerns can be influenced by negative (and often inaccurate) media reports.²¹ Media reports and inaccurate information could cause parents concern prior to getting their children vaccinated, specifically in regard to risk compensation.

Across several studies between 16% and 26% of parents indicate that they were concerned that HPV vaccination would increase the likelihood that their child would engage in riskier sexual behavior.²²⁻²⁵ However, this worry about sexual disinhibition was not usually listed as a reason for non-vaccination, and only 3–6% of parents cited this concern as a reason for refusing vaccination.^{26,27}

The objective of the present study was to conduct a systematic review of research literature to evaluate whether there is evidence (via either self-report of sexual behaviors or biological outcomes such as sexually transmitted infections) of sexual disinhibition following HPV vaccination. Our aims were to answer the following research questions: 1) Is there consistent, replicated evidence of increased self-reported risky sexual behaviors after HPV vaccination? and 2) Is there consistent, replicated evidence of increased incidence of sexually transmitted infections or pregnancies after HPV vaccination?

Results

Study characteristics

The initial search of the 3 databases resulted in 2,503 returns. Once duplicates were deleted, 1,584 articles remained. After screening by title and abstract, there were 29 full-text articles to be reviewed by all of the authors. The final selection resulted in 20 articles being included in the study. For the full PRISMA flow diagram, see [Figure 1](#).

Of the 20 studies included in the systematic review, 2 were qualitative, 12 were cross-sectional, and 8 were longitudinal studies. It is important to note that these categories are not mutually exclusive. If a study used more than one study design and the results were presented separately, it was counted in both relevant categories. Although we searched for studies between 2008 and 2015, the relevant studies for this review were published between 2011 and 2015. Furthermore, although we did not restrict by age or gender, all of the studies examined exclusively female populations and all of them studied populations within the 10 to 46 year-old age range. The descriptive statistics of the included studies are reported in [Table 1](#). The full list of qualitative, cross-sectional, and longitudinal study results from the review are included as [Tables 2, 3, and 4](#), respectively.

Critical appraisal of the studies

The 20 studies were divided among all of the co-authors, such that each study was reviewed by 2 co-authors, who then filled out corresponding data extraction sheets (the data extraction sheet used for this study is provided as the Appendix). The data extraction sheet contained items from previously validated data quality assessment tools including the Agency for Healthcare Research and Quality’s (AHRQ), Cochrane, PRISMA, and the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Items on the data extraction sheet included assessment of study design, inclusion/exclusion criteria, study population and comparison group, length of follow-up, outcomes, limitations, generalizability, and an assessment of overall study quality. Overall study quality was assessed by each coauthor on a scale of 1–10 with higher numbers indicating greater study quality. The authors were given criteria with which to judge the studies and if the quality assessment from each author varied by more than 2 points, disagreements were resolved through discussion. The study’s quality score was then averaged between the 2 reviewers’ scores. Average study quality score ranged from 1.8 to 9.0 (mean = 6.2; standard deviation = 2.0).

Behavioral outcomes

All but 3 studies examined self-reported behavioral outcomes ($n = 17$, 85%). A widely studied behavior was sexual activity, which was assessed in many of the studies included in the review ($n = 12$) but was only statistically evaluated in 10 of the studies. Sexual activity was defined differently across studies, and included reported sexual intercourse any time after receipt of HPV vaccine (or any time after 10 y of age for the unvaccinated controls),²⁸ ever having sex with someone of the opposite sex,²⁹ and any experience of intercourse.^{30,31} Other behaviors examined in the studies were: age at sexual debut ($n = 7$), number of sexual partners ($n = 13$), use of contraception ($n = 16$), and other sexual risk behaviors ($n = 5$).

Self-reported sexual activity

One study by Ajuo et al. (2014) used both qualitative and quantitative methods to examine self-reported sexual activity in 2 different communities (one vaccinated and one unvaccinated

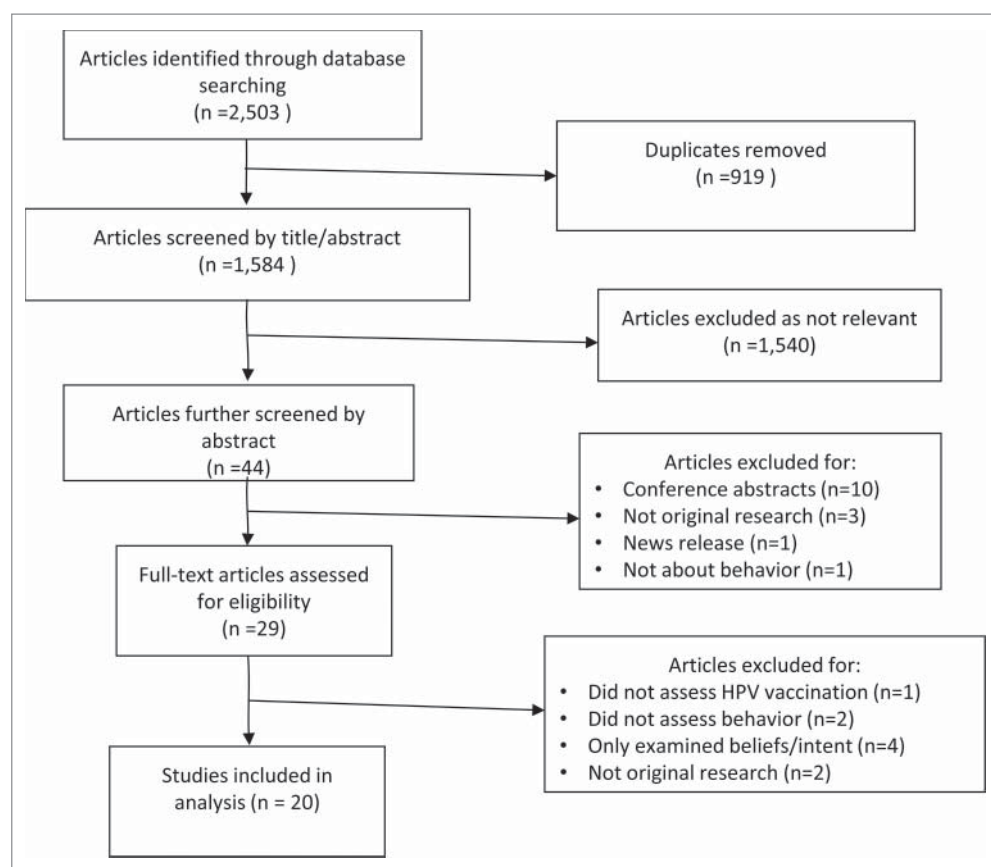


Figure 1. PRISMA flow diagram.

community) in Uganda.²⁸ The qualitative component of the study found that most girls indicated they were not engaged in sexual activity themselves but they knew of others who were. The cross-sectional survey portion of the study found that young girls engaged in sexual activity in both the vaccinated and unvaccinated districts, but vaccinated girls had a lower reported rate of sexual intercourse than unvaccinated girls (1.5% vs. 2.5%).²⁸

The majority of the studies examining self-reported sexual activity were cross-sectional in nature and some of these cross-sectional studies did find that vaccinated participants were more likely to have engaged in sexual intercourse than

unvaccinated participants.^{30,32,33} However, these studies also noted that many of their participants (between 45% and 62%) were sexually active prior to HPV vaccination.^{29,30} Due to the cross-sectional nature of these studies, these results may be more indicative of a woman engaging in sexual behavior and then seeking out protective measures as opposed to the vaccination causing the increased sexual behavior. Furthermore, previous studies have shown that providers are more likely to offer or strongly recommend the vaccine to patients they believe are sexually active or are not in a monogamous relationship.³⁴⁻³⁶ Other cross-sectional studies found no statistical difference in sexual activity between vaccinated and unvaccinated participants (odds ratios between 0.88 and 1.07).³⁷⁻⁴⁰

The longitudinal studies did not demonstrate that vaccinated women were more sexually active than unvaccinated women when post-vaccination behavior change was assessed. Some of these studies found that there was no statistically significant difference in baseline to follow-up sexual activity between vaccinated and unvaccinated women,^{37,41,42} while others found *decreases* in sexual activity after vaccination. One study of female sex workers conducted by Brown et al. (2013) in Peru found female sex workers decreased sexual activity with all clients after vaccination ($p < 0.001$).⁴³ And another study (Mayhew et al., 2014) of a fully vaccinated sample found that participants between 16 and 21 y of age who inappropriately perceived lower risk for non-HPV STIs after vaccination were actually less likely to initiate sex over the following 6 month period (OR = 0.13; 95% CI = 0.03–0.69).³¹

Table 1. Descriptive statistics and quality assessment.

Total Studies (20)	N (%)
Study Design	
Qualitative	2 (10%)
Cross-Sectional	12 (60%)
Cohort	8 (40%)
Used Unvaccinated Control Group	16 (80%)
Outcome Assessed	
Behavioral	17 (85%)
Reported Sexual Activity	12 (60%)
Age at Sexual Debut	7 (35%)
Number of Partners	13 (65%)
Contraception Use	16 (80%)
Biological	9 (45%)
STI Testing/Diagnosis	6 (30%)
Pregnancy/Abortion/Composite Measure	5 (25%)
Average Study Quality Score (1-10)	6.2

Table 2. Qualitative studies.

First author, year, location	Data collection method, date	Participant details	Analysis	Primary Findings
*Aujo, 2014, Uganda	Semi-structured focus groups, date unclear	52 girls aged 12-15 y old	Thematic analysis	Vaccinated and unvaccinated girls engaged in sexual activity. Effect vaccination might have on sexual behaviors had varying responses.
Ports, 2014, United States	Semi-structured individual phone interviews, 2013	30 women 19-25 y old (mean age=28.87), received all 3 HPV vaccine doses	Thematic analysis	83% said that having been vaccinated against HPV had no influence on their romantic relationships and did not have any effect on their participation in safer sex (50%). 27% reported that getting vaccinated made them more aware of sexually transmitted diseases, and more cautious with sexual activity.

* Aujo et al. (2014) utilized both qualitative and cross-sectional study designs and as such is listed in both tables. Only the results from the qualitative portion of the study are reported in this table.

Self-reported age at sexual debut

Seven of the studies examined age at first intercourse as a risky behavior post-vaccination. The studies defined the variable differently with some looking at age as a continuous variable and some categorizing the variable as sexual debut before or after a certain age (usually 15 or 16). Regardless of how the variable was defined, none of the studies that examined age at sexual debut found a statistically significant difference between vaccinated and unvaccinated groups.^{29,33,38,44-46} Only one study (Liddon et al., 2012) found an association between HPV vaccine and age at first intercourse. But this was only significant in the bivariate model of a subset of 20–24 y olds and was not significant in the multivariable model.³⁹

Self-reported number of sexual partners

Most of the studies examining the number of sexual partners between groups found no association between vaccination status and number of partners. This result held true in cross-sectional studies when the researchers examined number of lifetime partners,^{29,33,37-40,44,45} number of partners in the last 12 months,⁴⁴ and number of partners before 18 y of age.³⁸ It also held true in studies that followed cohorts longitudinally, which found vaccinated women did not have more sexual partners at follow-up.^{37,41,42} A Mayhew et al. (2014) study of a fully vaccinated sample did not see a significant increase in the number of sexual partners after the sample was vaccinated.³¹

In fact, some of the studies found that vaccinated women had fewer sexual partners than unvaccinated women. One population-based study of Nordic women (Hansen et al., 2014) found that women who were vaccinated opportunistically (i.e., those that were vaccinated but not during an organized vaccination program) were significantly less likely than unvaccinated participants to have had 4 or more partners before reaching age 18 (AOR = 0.56; 95% CI = 0.40-0.78).³⁸ A similar finding was reported in a study conducted by Sadler et al. (2015) in the United Kingdom that found that non-vaccination was positively associated with having 3 or more partners in the last 6 months (OR = 2.12; 95% CI = 1.08-4.17).⁴⁶ A study conducted by Lutringer-Magnin et al. (2013) in France, found that vaccinated girls between the ages of 17 and 20 had had fewer partners than unvaccinated girls ($p = 0.01$).⁴⁰ Furthermore, a

study of Peruvian female sex workers by Brown et al. (2013) found that participants had a significantly lower frequency of intercourse with new clients after vaccination ($p < 0.001$).⁴³

Use of contraception

Several of the studies examined use of contraception. Some assessed condom use while others examined use of hormonal contraception or counseling on contraception. While there has been some concern that an erroneous belief that the HPV vaccine protects against all STIs would result in a decrease in condom use, a study examining risk perceptions found that this erroneous belief did not result in decreased condom use.³¹ A qualitative study by Ports et al. (2014) found that none of the women they interviewed reported that the HPV vaccine had an influence on their use of condoms during sexual activity.⁴⁷ Cross-sectional studies assessing condom use utilized different definitions for their studies including an assessment of general condom use,^{30,44,45} consistent condom use in the last month,³⁹ condom use during most recent intercourse,⁴⁰ condom use during first intercourse,^{40,48} and consistent condom use during all sexual encounters.^{29,32,33,44} Regardless of how condom use was defined, none of the aforementioned studies found any statistically significant relationship between HPV vaccination and condom use. However, some studies did note that vaccinated women were more likely to take protective measures and found a positive association between condom use and vaccination. A study by Hansen et al. (2014) found that non-use of contraception during first intercourse was significantly less frequent among women who were vaccinated before sexual debut as opposed to their matched unvaccinated counterparts (OR=0.27; 95%CI=0.15-0.48 for those vaccinated during an organized vaccination program; OR=0.69; 95%CI=0.52-0.93 for those vaccinated opportunistically).³⁸ Liddon et al. (2012) found that a higher percentage of those who reported always or at least inconsistently using condoms reported being vaccinated as opposed to those who never used condoms.³⁹ Ruiz-Sternberg et al. (2014) reported a similar finding, that vaccinated women were more likely to report consistent condom use than unvaccinated women.³³ Additionally, Sadler et al. (2015) reported condom use at

Table 3. Cross-sectional studies.

First author, year, location	Study setting	Participant Details				Main findings
		Data collection method, date	Study population	Control population	Outcomes assessed	
*Aujo, 2014, Uganda	Two culturally similar districts in Uganda	Survey questionnaire, vaccination status verified through vaccine registry, date unclear	200 girls 12–15 y old (n = 12.8) from Nakasongola district, HPV vaccinated	200 girls 12–15 y old (n = 13.1) from Luwero district, HPV unvaccinated	Behavioral outcomes: Sexual intercourse any time from the time of HPV vaccination or any time from 10 y of age for unvaccinated	No significant differences were found between groups for sexual activity.
**Forster, 2012, United Kingdom	Schools in London and the South East England	Survey questionnaire, 2009	433 girls 16–17 y old (n = 17.1) from 4 schools that offered school-based HPV vaccination	620 girls 16–17 y old (n = 17.0) from 3 schools that did not offer school-based HPV vaccination	Behavioral outcomes: reported number of sexual partners, age at sexual debut	The group that had been offered the vaccine was not significantly more sexually active than the group that had not been offered the vaccine (41.2% vs 41.6%; OR = .98; 95%CI=0.7–1.4).
Hansen, 2014, Denmark, Norway, Sweden	Population registries	Self-administered structured questionnaire, 2011–2012. Sociodemographic data was obtained from Statistics Denmark, Statistics Norway and Statistics Sweden	3,805 women 18–46 y old, received HPV vaccine	40,247 women 18–46 y old, had not received HPV vaccine	Behavioral outcomes: age at first intercourse, non-use of contraception during first intercourse, the number of sexual partners	The rates of sexual debut and number of sexual partners did not differ significantly for women who were vaccinated before sexual debut and unvaccinated women. Vaccinated participants were less likely to have had 4+ partners before age 18 (AOR = 0.56; 95%CI = 0.40–0.78), and report non-use of contraception during first intercourse (AOR = 0.27; 95%CI = 0.15–0.48).
Liddon, 2012, United States	Nationally representative sample from US	National Survey of Family Growth, 2007–2008.	279 females 15–24 y old, received HPV vaccine	964 females 15–24 y old, had not received HPV vaccine	Behavioral outcomes: age at first sex (older or younger than 15), lifetime number of partners, consistent condom use in the past 4 weeks Biological outcomes: received STD service in the last year	No significant differences were found between groups for lifetime sex partners, consistent condom use in the past 4 weeks, and having received an STD service in the past year. Compared with those who reported never using a condom, participants always using a condom were more likely to report receipt of HPV vaccine (AOR = 3.0, 95%CI = 1.1–7.9).
Lutringer-Magnin, 2013, France	Primary care setting	Self-administered questionnaire, 2008–2009	135 females 14–23 y old, received HPV vaccine	181 females 14–23 y old, had not received HPV vaccine	Behavioral outcomes: Condom use (during first and most recent sexual intercourse), condom use behavior (non-risky, indeterminate, etc.), time in years from first sexual intercourse, number of partners, history of emergency, contraception, Biological outcomes: abortion, requests for HIV serology	No significant differences were found between groups for sexual activity, requests for HIV serology, history of abortions, or emergency hormonal contraception.
Marchand, 2013, United States	Community college	Web-based survey, 9/2011–11/2011	42 female students 18–26 y old, received any doses of HPV vaccine	72 female students 18–26 y old, had not received HPV vaccine	Behavioral outcomes: ever had sex with anyone of the opposite sex, age at first intercourse, number of partners in the last year, frequency of condom use in the last year	No significant differences were found between groups for any sexual behaviors including age at first intercourse (p=0.32), number of partners (p=0.97), or frequency of condom use (p=0.94) in either the bivariate or the multivariate analyses.

(Continued on next page)



Table 3. (Continued)

Participant Details						
First author, year, location	Study setting	Data collection method, date	Study population	Control population	Outcomes assessed	Main findings
Mather, 2012, Australia	Large university	Web-based survey, 5/2011–8/2011	119 women 18–29 y old (m = 19.2), received any doses of HPV vaccine	74 women 18–30 y old (m = 19.5), had not received HPV vaccine	Behavioral outcomes: condom use, monogamous for more than 3 months	Vaccinated participants were more likely to be sexually active (61.3%) than non-vaccinated participants (45.9%; $p < .05$). Among subsample of sexually active participants, no significant differences were found between groups for safer sexual behavior ($p = 0.84$) or consistent condom use ($p = 0.88$), after controlling for effects of age.
Mattebo, 2014, Sweden	Two municipalities	Written self-report questionnaire completed in classroom (n = 338) or via mail (n = 17), 1/2013–3/2013	227 girls 17–21 y old (median = 18), received any doses of HPV vaccine	121 girls 17–21 y old (median = 18), had not received HPV vaccine	Behavioral outcomes: experience of intercourse, condom use during oral sex, anal sex, protection during anal sex, group sex, friends-with-benefits relationship, one night stand. Biological outcomes: Self-reported history of STI diagnosis	No significant differences were found between groups for STIs, condom use ($p = 0.79$), oral sex ($p = 0.15$), anal sex ($p = 0.80$), group sex ($p = 0.80$). Vaccinated participants were more likely to have initiated intercourse (84%) than non-vaccinated participants (70%; $p < 0.005$). Vaccinated participants more likely to report a one night stand (41%) than non-vaccinated (29%; $p < 0.04$).
Ratanasiripong, 2014, United States	Public university	Web-based survey, Spring 2012	209 females 18–26 y old (m = 20.75 in total sample), received any doses of HPV vaccine	175 females 18–26 y old, had not received HPV vaccine	Behavioral outcomes: number of lifetime sex partners, number of sex partners in the last year, age at initiation, condom use.	No significant differences were found between groups for condom use ($p = .98$), lifetime sexual partners ($p = .39$), number of sexual partners in the last year ($p = .98$), number of partners before and after vaccination ($p = .07$).
Ruiz-Stenberg, 2014, Colombia	A private university and 3 private high schools	Self-administered survey, 5/2011–3/2012	506 women up to 26 y old (m = 19.6)	930 women up to 26 y old (m = 19.5)	Behavioral outcomes: ever had sex, initiation before 15 y old, more than 3 sex partners, condom use, contraception use	No significant differences were found between groups for initiation of sexual intercourse before 15 y of age ($p = 0.167$), number of sexual partners ($p = 0.381$), and use of alcohol or drugs at last intercourse ($p = 0.553$). Vaccinated adult women were more likely to have had sex (OR = 1.89) but also showed more consistent condom use (OR = 1.49), and contraception use (OR = 2.02).
Rysavy, 2014, United States	University hospitals and clinics	Computer assisted interviews, 2009–2011	153 girls 13–23 y old (m = 19.2), received HPV vaccination	70 girls 13–23 y old (m = 20.1), had not received HPV vaccine	Behavioral outcomes: Age at initiation, number of partners, condom use, age at anal and oral intercourse. Biological outcomes: STI diagnosis, pregnancy	No significant differences were found between groups for age at first intercourse ($p = 0.768$), number of partners ($p = 0.513$), condom use ($p = 0.407$), and STI diagnoses (p -values ranging from 0.242–0.763). Non-vaccination as associated with having been pregnant (20% vs 8.6%; $p = 0.016$) in bivariate analysis;

Table 3. (Continued)

First author, year, location	Study setting	Data collection method, date	Participant Details			Outcomes assessed	Main findings
			Study population	Control population	Outcomes assessed		
Sadler, 2015, United Kingdom	Genitourinary medicine clinics	Data collection method unclear, 9/2010–10/2011	231 women 14–20 y old (m = 18 for total sample), received at least one dose of the HPV vaccine	132 women 14–20 y old, unvaccinated	Behavioral outcomes: age at first intercourse, condom use, anal intercourse, drugs, alcohol, number of partners, emergency contraception use, sexual activity abroad Biological outcomes: history of abortion, received STI treatment, STI symptoms	however, this difference was not significant in multivariate regression. Non-vaccination positively associated with: having more than 3 partners in the last 6 months (OR = 2.12;95%CI = 1.08–4.17), attending the clinic with symptoms (OR = 1.78;95%CI = 1.09–2.92), having anal intercourse with their last sexual contact (OR = 4.34; 95%CI = 1.23–14.29) and receiving a positive C. trachomatis diagnosis from the clinic (OR = 2.3;95%CI = 1.06–5). Vaccination positively associated with condom use at first intercourse (OR = 0.55; 95%CI = 0.32–0.96).	

* Aujo et al. (2014) utilized both qualitative and cross-sectional study designs and as such is listed in both tables. Only the results from the cross-sectional portion of the study are reported in this table.

** Forster et al. (2012) utilized both cross-sectional and longitudinal study designs and as such is listed in both tables. Only the results from the cross-sectional portion of the study are reported in this table.



Table 4. Longitudinal studies.

First author, year, location	Study setting	Data collection method, date	Participant Details			Outcomes assessed	Length of Follow-Up	Main findings
			Study population	Control population	Outcomes assessed			
Al Romaih, 2011, United States	Adolescent medicine clinics	Chart audits; date not reported	499 female adolescents, (mean age=16.05), all vaccinated	Pre-, post- design, each participant served as her own control	Behavioral outcomes: self-reported sexual activity and number of sexual partners	Outcome was assessed prior to vaccination (at an unspecified time interval), at vaccination, and one-year post vaccination.	No significant differences in reported sexual activity or number of partners before and after vaccination. No statistical analysis reported.	
Bednarczyk, 2012, United States	Large managed care organization	Electronic medical record audits, 2006–2007, follow-up through 2010	493 females 11–12 y old (m = 11.9), received at least 1 HPV vaccine	905 females 11–12 y old (m = 11.6), received no HPV vaccines	Biological outcomes: "Testing/Diagnosis/Counseling" (any occurrence of testing for C. trachomatis or pregnancy; diagnoses of C. trachomatis infection, pregnancy, or VD-NOS; and physician counseling on contraceptives). "Diagnosis Only" (any occurrence of diagnostic outcomes for C. trachomatis infection, pregnancy, or VD-NOS)	3 y retrospective	No significantly increased incident rate ratios were found for outcomes comparing HPV vaccine-exposed and unexposed girls. This includes STI testing/diagnosis (IR=1.29; 95%CI=0.92–1.80), and pregnancies (IR=1.89; 95% CI=0.33–10.79).	
Brown, 2013, Peru	Non-governmental organization clinic	Sequential survey data; date not reported	200 female sex workers, 18–26 y old (m = 22.9), all received at least 1 HPV vaccine	No comparison group	Behavioral outcomes: reported sex with new clients, reported condom use	7 months prospective	Reported sexual activity with all clients decreased significantly from day 0 to month 7 (p < 0.001). Frequency of reported intercourses with new clients over the same time period was lower (p < 0.001). Reported condom use with all clients and with non-paying partners did not change over time. Number of FSWs having nonpaying sexual partners increased significantly (OR = 3.96; 95%CI=1.88-8.35) as did frequency of intercourse with non-paying sexual partners (p < 0.001).	
Cummings, 2012, United States	Urban primary care clinics	Study population-questionnaire, in-person interview, self-collected vaginal swab; 2010 Controls-questionnaire, in-person interview, clinician obtained or self-collected vaginal swab; 1999–2005	75 females 14–17 y old (m = 15.5), received at least 1 HPV vaccine	150 females (2:1 match) 14–17 y old (m = 15.3), unvaccinated	Behavioral outcomes: number of sex partners in the last 2 months, frequency of sexual activity, condom use; Biological outcomes: Gonorrhea, chlamydia, trichomonas diagnoses, HPV-type prevalence.	Comparison group: 2 y retrospective Study population: one-time questionnaire	Instances of vaginal intercourse without a condom (over the last 2 months) were significantly lower in the vaccinated as compared to those in the unvaccinated (p < 0.001). This was the only sexual behavior found to be different between the 2 cohorts. No significant differences were found in chlamydia and trichomoniasis rates between the unvaccinated and vaccinated cohorts.	

Table 4. (Continued)

First author, year, location	Study setting	Data collection method, date	Participant Details			Outcomes assessed	Length of Follow-Up	Main findings
			Study population	Control population	Outcomes assessed			
**Forster, 2012, United Kingdom	Schools in South East England	Sequential survey data, 2009–2010	148 females 16–17 y old (m = 17.5), received at least one HPV vaccine	259 females 16–17 y old (m = 17.5), received no HPV vaccines	Behavioral outcomes: sexual debut, number of sex partners, condom use	6 months prospective	The change in the proportion of girls who were sexually active from baseline to follow-up was not significantly greater in the vaccinated group than the unvaccinated group OR=0.80; 95%CI=0.04–1.59). The change in number of sexual partners from baseline to follow-up was not significantly different between groups (p = 0.38). Change in condom use between baseline and follow-up did not differ by vaccination group (OR=0.88; 95% CI = 0.58–1.33).	
Jena, 2015, United States	Large insurance database	Medical and pharmaceutical claims, 2005–2010	21,610 females 12–18 y old (m = 15.0), vaccinated against HPV	n=186,501 age-matched females 12–18 y old (m = 14.9), not vaccinated against HPV	Biological outcomes: at least one medical claim for any of the following: chlamydia, gonorrhea, herpes, human immunodeficiency virus or AIDS, or syphilis.	One year before vaccination to one year after vaccination	The rates of STIs in the year before vaccination were higher among HPV-vaccinated females compared with age-matched non-vaccinated females (AOR=1.37; 95% CI = 1.09–1.71). The rates of STIs increased for the vaccinated and non-vaccinated groups in the year after vaccination. The difference-in-difference odds ratio was 1.05 (95% CI = 0.80–1.38), implying that HPV vaccination was not associated with an increase in STIs. Similar associations held among age subgroups.	
Mayhew, 2014, United States	Hospital-based adolescent primary care center	Sequential survey data, date not reported	339 females 13–21 y old (m = 16.8), received at least one HPV vaccine	No comparison group	Behavioral outcomes: initiation of sexual intercourse, perceived risk for STIs other than HPV after vaccination, perceived need for safer sexual behaviors after vaccination, sexual behaviors at 2 and 6 month follow up appointments. For sexually inexperienced at baseline: sexual initiation. For sexually experienced at baseline: number of sexual partners, condom use at last intercourse.	6 months prospective	No significant associations between risk perceptions and subsequent sexual behaviors among all sexually inexperienced and all sexually experienced participants (p=0.59). In age-stratified analyses of sexually inexperienced participants: those 16 to 21 y of age who had higher scores on the scale measuring perceived risk for STIs other than HPV, indicating lower perceived risk for other STI (an inappropriate perception) were less likely to initiate sex over the next 6 months. (OR=0.13; 95%CI=0.03–0.69).	

(Continued on next page)

Table 4. (Continued)

First author, year, location	Study setting	Data collection method, date	Participant Details			Length of Follow-Up	Main findings
			Study population	Control population	Outcomes assessed		
Smith, 2015, Canada	Ontario's health database	Audit of population-based administrative database	128,712 females, 13–17 y old (n = 13,17 for total sample at cohort entry), not eligible for the HPV vaccination program	131,781 females, 13–15 y old (n = 13,17 for total sample at cohort entry), not eligible for HPV vaccination program	Biological outcomes: a composite measure of incident pregnancy and non-HPV-related sexually transmitted infections. These were also assessed separately.	4 y (grade 8 to grade 12)	Controlling for birth timing in the year, no statistically significant increase in risk of the composite measure (OR=0.98; 95% CI=0.84–1.14), pregnancy (OR=1.00; 95% CI=0.83–1.21), or STIs (OR=0.81; 95% CI=0.63–1.04) in relation to HPV vaccination.

**Forster et al. (2012) utilized both cross-sectional and longitudinal study designs and as such is listed in both tables. Only the results from the longitudinal portion of the study are reported in this table.

first intercourse was positively associated with HPV vaccination (OR = 0.55; 95%CI = 0.32-0.96).⁴⁸ There were 2 studies that examined use of emergency hormonal contraception (Lutringer-Magnin et al., 2013 and Sadler et al., 2015). Neither study found any differences in the use of emergency contraception between those who had been vaccinated and those who had not.^{40,48}

Contraceptive behavior was also examined by several studies longitudinally. Bednarczyk et al. (2012) used data from a managed care organization to assess the relationship between a patient seeking counseling on contraceptives and HPV vaccine. This study found that vaccinated participants were more likely to seek counseling on contraceptive use as opposed to unvaccinated participants, although the adjusted incident rate ratio was not significant (OR=2.31; 95%CI = 0.99-5.38).⁴⁹ This result is consistent with a study by Forster et al. (2012) that found no change in condom use from baseline to follow up by vaccination group (OR=0.88; 95%CI = 0.58-1.33).³⁷ A study of female sex workers found no change in condom use with all clients after vaccination but they did note that condom use with non-paying partners increased, although not significantly ($p = 0.38$).⁴³ Another longitudinal study (Cummings et al., 2012) found instances of vaginal intercourse without a condom over the last 2 months was significantly lower in the vaccinated group ($p < 0.001$).⁴¹ The findings from all of the studies combined demonstrated that there was either no association between HPV vaccination and condom use/contraception counseling or they demonstrated that vaccinated participants engaged in safer behaviors than unvaccinated participants.

Other risk behaviors

Many of the included studies also examined risky behaviors that did not fit in the above categories. Several of the studies examined relationship status. Most of them defined being in a monogamous relationship as a “safe” behavior and being in non-exclusive relationships or having one-night stands as constituting “unsafe” behavior. One study conducted in Uganda that used dating and sexual activity as measures of risky behavior found that unvaccinated girls were dating at higher rates than vaccinated girls (5% vs. 2.5%) but the authors did not assess if those specific dating relationships involved risky sexual behaviors.²⁸ Another study (Mather et al., 2012) compared “safe sexual behavior” between vaccinated and unvaccinated individuals by creating a composite measure that included condom use, use of other contraception, and having been in a monogamous relationship for at least 3 months. Using this measure, authors found no relationship between HPV vaccination and engaging in safe sexual behavior.³² Rysavy et al. (2014) used a similar technique to examine “high risk sexual behaviors” such as frequency of condom use, number of partners, as well as experience of anal and oral intercourse and age at first anal and oral intercourse to create a risk behavior score. This study found that there were no differences between the vaccinated and unvaccinated groups on the composite risk behavior score.⁴⁵ This relationship was still not significant when the high risk behaviors were examined individually. Another study (Mattebo et al., 2014) examined high risk behaviors individually and assessed the effect of experiencing one-night stands, group sex, “friends with benefits” relationships, oral sex, and

anal sex. In this study the authors did find that vaccinated women were more likely to have experienced a one-night stand ($p = 0.046$) but this cross-sectional study noted that 62% of their sample had reached sexual debut before vaccination so the temporal relationship between sexual experience and vaccination cannot be assessed and it is possible a person engaging in high-risk sexual behaviors was more likely to seek vaccination.³⁰ Furthermore, this study found no differences when comparing vaccinated and unvaccinated individuals with respect to experiencing a “friends with benefits” relationship, group sex, giving oral sex, receiving oral sex, or anal sex.³⁰ Lastly, a cross-sectional study examined several risk behaviors including anal intercourse, sexual experiences abroad, use of drugs or alcohol, and being a current smoker. Among other risk behaviors previously discussed (i.e., contraception use, number of partners, etc.) this study found that the unvaccinated group was more likely to have experienced anal intercourse as their last sexual contact (OR = 4.43; 95%CI = 1.23-14.29) and to be a current smoker.⁴⁸ Smoking status is an important factor to examine because smoking is a risk factor for cervical cancer, even when controlling for the effects of HPV infection and other potential cofactors.^{50,51}

Biological outcomes

Along with reporting behavioral outcomes, several studies also examined biological outcomes ($n = 9$, 45%). For the purposes of this review, they have been divided into two general categories: STI testing/diagnosis and pregnancy (including a composite measure of STI and pregnancy)/abortions.

STI/HIV testing or diagnosis

All of the studies in this subset had some measure of STI testing or diagnosis. Of the studies that examined STI or HIV testing or diagnosis, none of them found HPV vaccination to increase STI rates. Of the cross-sectional studies, one (Liddon et al., 2012) found no association between HPV vaccination and receiving STI services in the past year in both the 15-19 and the 20-24 y old age groups.³⁹ Two cross-sectional studies examining reported STI diagnoses^{30,45} and one examining HIV serology⁴⁸ all found no significant differences between the vaccinated and unvaccinated groups. Additionally, one study (Sadler et al., 2015) found that unvaccinated women were more likely to have received a positive Chlamydia trachomatis diagnosis (OR = 2.3; 95% CI = 1.06-5.00).⁴⁸

Two longitudinal studies (Cummings et al., 2012 and Jena et al., 2015) examined the association between STIs and HPV vaccination.^{41,52} One longitudinal study by Jena et al. (2015) found that the difference-in-difference odds ratios in the year after vaccination was similar between the vaccinated and unvaccinated groups.⁵² This held true for both the 12 to 14 and the 15 to 18 year-old groups. Another cohort study found no differences in Chlamydia or Trichomonas infection rates between vaccinated and matched unvaccinated groups.⁴¹

Abortion/Pregnancy or a composite measure of STI and pregnancy

Several studies used composite measures of STI diagnosis and pregnancies. One cohort study (Bednarczyk et al., 2012) looked

at a composite measure of testing or diagnosis of Chlamydia trachomatis infection, pregnancy, or venereal disease not otherwise specified (referred to as testing/diagnosis/counseling) found that girls receiving HPV vaccine did not have significantly higher rates of testing/diagnosis/counseling. They found the same results when they examined diagnosis-only rates between vaccinated and unvaccinated groups.⁴⁹ Another cohort study (Smith et al., 2015) found no statistically significant increase in a composite measure of STIs and pregnancy in relation to HPV vaccination. This result held true when STIs and pregnancy were examined separately as well.⁵³

Studies also examined pregnancy and abortions individually. Sadler et al. (2015) found no association between vaccination status and abortion ($p = 0.85$).⁴⁸ Another (Lutringer-Magnin et al., 2013) assessed abortion rates between vaccinated and unvaccinated groups found that 7.1% of their population had had an abortion and all of these participants were unvaccinated.⁴⁰ Additionally, a study with a population between 13 and 23 y of age found that unvaccinated women were more likely to have been pregnant (20% vs. 8.6%, $p = 0.016$), a result that runs contrary to the notion of risk compensation.⁴⁵

Discussion

There have been several studies examining the association between HPV vaccination using self-report or biological markers of increased risky sexual behaviors. Twenty studies were identified for this systematic review. The included studies were all published between 2011 and 2015 and varied in study design and sample size. Each of the studies had limitations and the results of each individual research effort should be interpreted with caution. However, when this body of literature is examined as a whole, with similar findings reported across studies, the consistent and replicated evidence indicates that HPV vaccination does not lead to risk compensation/sexual disinhibition. The finding that adolescents do not appear to respond to vaccination with increased risky sexual behavior suggests no support for RHT as applied to HPV vaccination. This conclusion is supported both by studies that focused on self-reported sexual behavior as well as studies that examined biological markers of risk (e.g., STI diagnosis).

Furthermore, there appeared to be more support for the fact that vaccinated women actually showed less involvement in risky behaviors than unvaccinated women, which was evidenced by lower numbers of sexual partners and increased use of contraception. This finding is not entirely surprising in light of previous research reporting that pro-health behaviors tend to cluster together, such that a person who engages in one protective health behavior (e.g., getting vaccinated) is more likely to engage in another (e.g., using condoms).⁵⁴ Additionally, an HPV vaccination visit to a healthcare provider may present families and providers with opportunities to discuss and promote health and disease prevention behaviors.

Several studies that examined risk perception merit discussion, even though they did not meet the inclusion criteria for the systematic review, and therefore were not presented in the Results section. Some of these studies examined the perception of risk in a completely vaccinated sample and compared a decreased risk perception post-vaccination to

subsequent sexual behaviors. These studies found that vaccinated individuals perceived a need for safer sexual behavior after vaccination.⁵⁵⁻⁵⁷ It is notable that these studies' findings were consistent with the results of studies included in this review. Furthermore, authors of a recent review of the literature on HPV vaccine attitudes and uptake found that the concern about risk compensation following vaccination was a "myth" rather than a valid concern.⁵⁸

This systematic review does have limitations so conclusions must be drawn with caution. First, the studies included are heterogeneous in both population and outcome definitions, which could reduce the specificity and precision of the findings. This issue is common in systematic reviews of this nature. For instance, one recent systematic review examining HPV vaccination or vaccine intent found varied evidence between HPV vaccination or vaccine intent and sexual behavior primarily due to the heterogeneous nature of the included studies.⁵⁹ At the same time, the fact that similar results are reported across studies that varied so widely in methodology and population, suggests that the findings of no association between vaccination and sexual risk compensation are robust. Secondly, the desire to engage in risky sexual behavior might cause a person to seek out vaccination which would make it appear that the vaccinated group practices more risky sexual behavior. This can be difficult to assess, particularly in cross-sectional studies because, as some research has shown, there are times when physicians have vaccinated their patients based on perceived risk status.³⁴⁻³⁶ This should not be confused with an implication that the vaccination is the *cause* of the risky behavior. Finally, this review of the literature is reliant on the findings of the studies included in the review. Each of these individual studies had limitations of their own including: a lack of a comparison group, recall bias, and social desirability of responses among others. Nevertheless, this study thoroughly examined 3 different databases with relevant search terms in order to capture the appropriate studies. To our knowledge, this is the first systematic review examining the association (or lack thereof) between HPV vaccination and subsequent sexual behaviors and adds credibility to the literature by combining the results and showing there is no consistent, replicated evidence of sexual disinhibition after HPV vaccination.

Materials and methods

A systematic review of the literature was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol and searching the PubMed, CINAHL, and Embase databases. The following search terms were used: [(sex behavior OR sex behavior OR sexual) AND (human papillomavirus OR HPV) AND (vaccines OR vaccine OR vaccination)] and the results were limited to studies from January 1, 2008 to June 30, 2015. The January 1, 2008 start date was chosen in order to capture articles examining behaviors post-vaccination. 4vHPV was first licensed in the US in mid-2006 and the Advisory Committee on Immunization Practices (ACIP) voted to routinely recommend it for girls in June 2006, at which point it was covered by the majority of insurers.⁶⁰ These recommendations were published in the Morbidity and Mortality Weekly Report in March 2007.⁶¹ Therefore, relevant

research examining post-vaccination behaviors was not published until 2010. Nevertheless, the 2008 start date for the search was chosen as a conservative estimate in order to ensure that we captured all relevant research.

To answer the outlined research questions, study outcomes were divided into 2 groups: self-reported behaviors (age at sexual initiation, reported number of sexual partners, and reported condom usage), and biological outcomes (pregnancy and STI diagnoses). Articles were included if they examined reported behaviors and/or biological outcomes post-vaccination. Studies were not restricted by age, gender, or geographic location. Articles were excluded if they examined worry or behavioral intent but not actual behaviors. Studies were also excluded if they were not original, peer-reviewed research articles (e.g. published abstracts for conferences, press releases, or commentaries on other articles).

First, studies were screened for inclusion by reviewing the titles and abstracts (MLK & GKS). Additional studies were excluded by a closer examination of the remaining abstracts (MLK & GDZ). The remaining studies were examined as full-text articles. Two authors independently reviewed each study to determine the relevance for inclusion. Each reviewer completed a data extraction and quality assessment sheet for each article. Most of the quality assessment tools for systematic reviews were developed and validated for intervention research.⁶²⁻⁶⁵ The data extraction sheet used in this systematic review was developed by combining relevant portions of previously validated data quality assessment tools from the Agency for Healthcare Research and Quality's (AHRQ), Cochrane, PRISMA, and the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

Conclusion

The consistent, replicated evidence found across the 20 studies examined in this systematic review provides a strong body of evidence refuting that there is an association between HPV vaccination and risky sexual behavior. The 20 different studies, utilizing at least 4 distinct study designs, and including a total of 521,879 participants, found no evidence of increased numbers of sexual partners, younger age of sexual initiation, decreased use of contraception (including both condoms and hormonal contraceptives), increased STI diagnoses, increased pregnancy rates, or increased history of abortion among those vaccinated against HPV. In fact, some studies found vaccinated women showed *lower* risky behaviors than unvaccinated women, indicating a tendency toward less risky health behaviors. These findings should alleviate parental and provider concerns that HPV vaccination will lead to risky sexual behaviors. Furthermore, as others have noted, even if risk compensation was identified as an issue related to HPV vaccination, this would not be justification for withholding vaccination, but would argue for effective pre- and post-vaccination counseling.⁵⁸

Disclosure of potential conflicts of interest

Dr. Kahn chaired the review committee for a grant to the Society for Adolescent Health and Medicine evaluating public health demonstration

project proposals to improve adolescent vaccination; grant funding for this program was from Merck, Inc. Dr. Kahn co-chaired two HPV vaccine clinical trials in HIV-positive individuals, for which Merck & Co., Inc., provided vaccine and immunogenicity titers. Dr. Rosberger has served as a consultant for Merck at a meeting in October 2015 and as a lecturer to family physicians in April 2015. Dr. Zimet is an investigator on investigator-initiated research funded by Merck and by Roche and he served as a consultant to Merck in 2014.

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Appendix. Observational study data extraction sheet for behavioral outcomes

Authors:		Title:		Year published: Year data collected:	
Journal:		Extracted by:	Date extracted:	Qualitative or quantitative:	
Study type: Qualitative: Focus groups/In-person interviews/Structured interviews Quantitative: Cohort/Case Control/Cross-Sectional; Matched/Unmatched					
Research question/study aims: As stated by the authors. .					
Study Setting: Geographic location (including city/country), as well as a description of the location where the data were collected.		Study population description (and sample size):		Comparison population description (and sample size):	
Inclusion criteria:					
Exclusion criteria:					
Outcome assessed:			Outcome measurement tool:		
Time-frame/Length of follow-up:			Possible biases of the study:		
Statistical/ analytical methods:					
Study Limitations:					
Main results:					
Interpretation:			Generalizability:		
Overall strength of evidence to refute evidence of risk compensation (scale of 1-10):					
Additional notes:					