

## Review Article



# HPV vaccination among seropositive, DNA negative cohorts: a systematic review & meta-analysis

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### Trial Registration

PROSPERO Identifier: [CRD42020206888](https://www.crd.org/CRD42020206888)

### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

## ABSTRACT

**Objective:** Vaccine efficacy among previously exposed, but currently uninfected women, i.e., those who have serological evidence of a prior human papillomavirus (HPV) infection without corresponding detectable HPV DNA, remains incompletely defined. This meta-analysis assessed the serotype-specific efficacy of prophylactic HPV vaccination against HPV16/18 persistent infection (PI) and cervical intraepithelial neoplasia (CIN) among seropositive, DNA negative (SPDN) women enrolled to randomized controlled trials (RCTs) of HPV L1-based vaccines.

**Methods:** Searches were conducted on 08/16/20 on MEDLINE, Embase, Scopus and CENTRAL. RCTs of L1-based prophylactic bivalent or quadrivalent HPV vaccines, reporting serotype-specific clinical efficacy endpoints in the HPV16/18 seropositive, DNA-negative populations were included. Relative risks (RRs) of 6-month PI (6mPI), 12-month PI (12mPI), CIN1+ and CIN2+ were pooled using a random-effects model.

**Results:** A total of 1,727 citations were reviewed. 8 studies, with a total of 9,569 SPDN participants, met all eligibility criteria. The RR of 6mPI (RR=0.22; 95% confidence interval [CI]=0.08–0.61; p=0.018), 12mPI (RR=0.20; 95% CI=0.05–0.80; p=0.035), CIN1+ (RR=0.13; 95% CI=0.05–0.30; p=0.003) and CIN2+ (RR=0.15; 95% CI=0.04–0.59; p=0.022) was significantly reduced in the vaccinated compared to the unvaccinated group.

**Conclusion:** Our findings suggest high serotype-specific efficacy for HPV vaccination among cohorts of women with evidence of prior HPV16/18 infections, including 87% efficacy (95% CI=70%–95%; p=0.003) against HPV16/18 cervical dysplasia. HPV vaccination is highly effective among uninfected women, regardless of prior exposure history.

**Trial Registration:** PROSPERO Identifier: [CRD42020206888](https://www.crd.org/CRD42020206888)

**Keywords:** Uterine Cervical Neoplasms; Human Papillomavirus 16; Human Papillomavirus 18; Vaccination

## INTRODUCTION

Despite significant progress in the understanding and treatment of human papillomavirus (HPV)-associated malignancies, improvements in cancer screening [1,2], and the advent of prophylactic vaccines, cervical cancer remains a leading cause of cancer related morbidity

**Author Contributions**

Conceptualization: C.M.E.; Data curation: C.M.E., R.P.; Formal analysis: C.M.E., R.P., I.P.; Investigation: C.M.E., R.P.; Methodology: C.M.E., R.P.; Project administration: C.M.E., R.P., D.B.; Resources: C.M.E.; Supervision: C.M.E., I.P., D.B.; Validation: C.M.E., I.P., D.B.; Visualization: C.M.E., R.P.; Writing - original draft: C.M.E., R.P.; Writing - review & editing: C.M.E., D.B.

and mortality worldwide, particularly affecting women in low-to-middle income countries [3]. Persistent infection with high-risk HPV (hrHPV) is responsible for virtually all [4] of the approximately 570,000 global cases of cervical cancer and 311,000 global deaths annually [3].

Three prophylactic HPV vaccines, Cervarix® (GlaxoSmithKline, Brentford, UK), Gardasil® (Merck, Kenilworth, NJ, USA) and Gardasil9® (Merck) are in widespread clinical use [5]; the principal use of these vaccines is in the prevention of cervical intraepithelial neoplasia (CIN) 3, AIS, or invasive cervical malignancy requiring surgical or multimodal treatment. Prophylactic HPV vaccines consist of recombinant HPV L1 capsid protein virus-like particles [5], and have been demonstrated to be highly immunogenic, clinically effective, and safe in preventing incident cervical infection with vaccine-type HPV strains and the cytopathological sequelae of such infections [6-10]. Over one hundred countries have adopted HPV L1-based vaccination as part of national vaccine programs [11], and epidemiological studies demonstrate a falling incidence of cervical cancer, cervical dysplasia, and other non-malignant HPV-associated diseases such as genital warts, among vaccinated populations [10,12-14]. Non-L1 based, and therapeutic vaccines, have not demonstrated sufficient efficacy to justify adoption in routine clinical practice, despite promising research in this area [15].

The incidence of HPV infection rises rapidly after sexual debut [16-18]. The majority of hrHPV infections are characterised by indolent transient infection followed by spontaneous clinical clearance (DNA non-detectability), within two years [19-21]. Consistent evidence demonstrates that efficacy of L1-based vaccines is greatest when administered in adolescence or to women who are naïve to HPV [6]. In established, DNA detectable infection, vaccination does not reduce progression to cervical dysplasia [6,22-25], although some moderate-level evidence supports the use of vaccination when administered prior to, or following, ablative surgical procedures [26,27].

Accurate estimates of vaccine efficacy (VE) among seropositive, DNA negative (SPDN) populations is of particular relevance in the context of primary HPV screening modalities which provide HPV DNA status in routine clinical practice [1,2]. HPV-based screening may present physicians with uncertainty as to how to advise individual women with a personal history of HPV infection, whose screening no longer detects HPV DNA. Although prophylactic HPV vaccination is approved on an individual basis up to the age of 45 by the FDA [28], efficacy among such previously exposed, currently uninfected, subjects (defined by seropositivity to type-specific HPV IgG without corresponding DNA positivity, i.e., SPDN), remains incompletely defined.

This paper summarises published data regarding the efficacy of L1-based HPV16/18 vaccination against 6-month persistent infection (6mPI), 12-month persistent infection (12mPI), HPV16/18 associated CIN 1 or worse (CIN1+), and HPV16/18 associated CIN 2 or worse (CIN2+) among populations of SPDN women enrolled to randomised controlled trials of HPV L1-based vaccines. All CIN endpoint determinations included assessment of the causative HPV serotype. Data was collected from published materials, including primary study subgroup analyses, clinical study reports, publication supplements, and from a prior post-trial cohort study. To our knowledge, this paper represents the first meta-analysis of published data for VE among HPV SPDN populations.

## METHODS

This study was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA). The PRISMA checklist can be found in the **Data S1**. The protocol for this systematic review was prospectively registered on PROSPERO (CRD42020206888) and can be found in the **Data S1**.

### 1. Search strategy

A search was carried out on MEDLINE (PubMed), Embase, Scopus, Cochrane Central Register of Controlled Trials for studies published between 1 January 2000 and August 2020. The search strategy included medical subject heading, free text words and synonyms covering 'HPV', 'vaccine' and 'trials', and was restricted to studies in English and conducted in humans. The full search strategy is available in the **Data S1**. References from other relevant systematic reviews [6,29] were hand-searched for additional studies. Duplicate records were removed using the Covidence systematic review manager.

### 2. Screening and article selection

Two independent authors (RP & CME) reviewed titles and abstracts to identify relevant studies. Full-text manuscripts and relevant study supplements (**Data S1**) were assessed independently by 2 reviewers (RP and CME) against predefined inclusion criteria: randomised controlled trials of prophylactic HPV vaccination versus placebo/other non-HPV vaccine comparator, reporting efficacy among patients that were seropositive to HPV16 and/or HPV18 but cervical DNA-negative to the corresponding serotype(s) at enrolment.

Trials that included either bivalent (HPV16/18, Cervarix<sup>®</sup>) or quadrivalent (HPV16/18/6/11, Gardasil<sup>®</sup>) were included. The single large RCT of the nonavalent Gardasil9<sup>®</sup> vaccine [30] was excluded as it was assessed against a quadrivalent vaccine comparator, precluding assessment of HPV16/18 endpoints. Case reports, case series, observational studies, conference abstracts, commentaries, and editorials were excluded. Trials that reported efficacy only in men and HIV positive cohorts, those with endpoints other than cervical dysplasia, and those that concerned therapeutic HPV vaccination or non-L1 based vaccines were excluded. Any disagreement between reviewers was resolved by discussion until consensus was reached. The study selection procedure is presented using a PRISMA flowchart (**Fig. 1**). Where efficacy of the seropositive, DNA-negative cohort was not reported in the manuscript or the **Data S1**, clinical study reports, where available, were reviewed.

### 3. Data extraction

Two authors (RP & CME) independently extracted data. Detailed references to included data are provided in the **Data S2** as a spreadsheet file. Conflicts were resolved by discussion, and findings were reported in accordance with PRISMA guidelines. Data were extracted using Microsoft Excel in a standardised proforma under the following headings: Sponsor ID; clinicaltrials.gov trial number; year of publication; study location; study period; inclusion criteria including age range, pap smear at enrolment and number of sexual partners; definition of HPV seropositivity including laboratory technique and titres threshold; definition of HPV DNA negativity; intervention; control; whether total vaccinated cohort or according to protocol analyses were used; total enrolment; total individuals that were seropositive and DNA negative to HPV16/18. The number of events in the intervention and control arm was extracted for endpoints including HPV16/18-associated 6mPI; 12mPI; CIN1+ and CIN2+. HPV-16 and HPV-18 endpoints were independently assessed in all included studies.

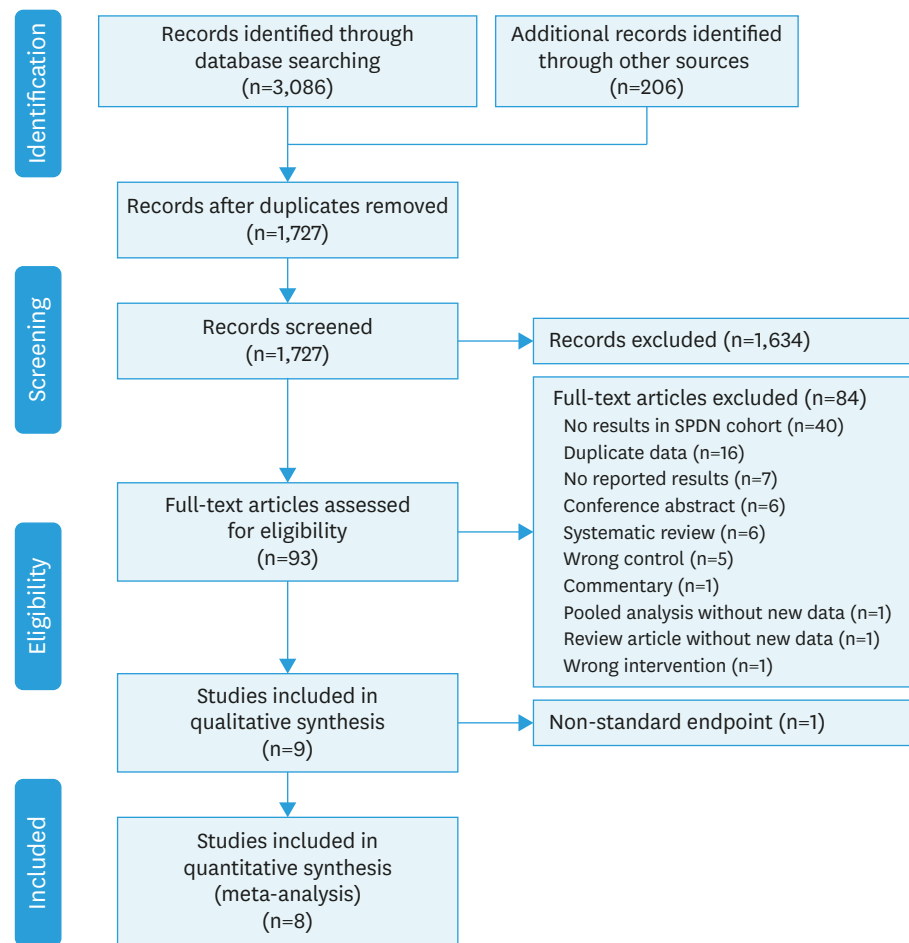


Fig. 1. PRISMA flowchart of search strategy.

#### 4. Assessment of bias

The risk of bias in included RCTs was assessed using Cochrane's Risk of Bias Tool and the criteria specified in the Cochrane Handbook for Systematic Reviews of Interventions [31]. This included assessment of the randomisation process, deviations from intended intervention, missing outcome data, measurement of outcome, and selection of the reported result. Results are presented in both a risk of bias chart and a risk of bias summary.

#### 5. Statistical analysis

Relative risk (RR) for 6-moPI, 12-moPI, CIN1+ and CIN2+ in the intervention (SPDN-vaccinated) versus the control arm (SPDN-unvaccinated), were calculated along with 95% confidence intervals (95% CIs). As the true effect was expected to vary between populations, the results were pooled using a random-effect model, employing the Mantel-Haenszel method [32]. VE was estimated using the formula:  $VE = 1 - RR$ . The number needed to vaccinate (NNV) was calculated using the formula  $NNV = 1/\text{Risk Difference}$  [31]. Heterogeneity was assessed both graphically using Forest plots, as well as Cochran's Q test and the  $I^2$  statistic [33]. Prespecified subgroup analyses using the type of vaccine as an independent variable were carried out to explore sources of heterogeneity. Sensitivity analyses were undertaken to explore the effect of studies with a higher risk of bias and the effect of each individual study on the overall pooled estimate. Statistical analysis was carried out using R version 4.0.2 packages *meta*, *metafor*, and *dmetar*.

## RESULTS

### 1. Identified studies

#### Study design and participants

Our original search identified 3,086 studies. 206 studies were added from the references of two other systematic reviews [6,29]. After removal of duplicates, 1,727 studies remained; 1,634 of these were excluded following title and abstract screening (Fig. 1). Of the 93 remaining articles, 40 did not separately report efficacy in the SPDN subgroup in either the manuscript, **Data S1** or publicly available clinical study report. Otherwise, 16 articles represented duplicate data, 7 did not report results, 6 were conference abstracts, 6 were systematic reviews, 5 did not have a placebo control arm, 1 was a commentary, 1 was a pooled analysis with no new data, 1 was a review, and 1 had the wrong intervention. One study had a non-standard endpoint of 4-year point prevalence, and was included for discussion in the narrative synthesis, but not in the meta-analysis [34].

A summary of study characteristics can be found in **Table 1**. A total of eight studies matched all the eligibility criteria for inclusion in the meta-analysis. Four studies evaluated the bivalent HPV16/18 vaccine (Cervarix®) while four studies evaluated the quadrivalent HPV6/11/16/18 vaccine (Gardasil®). All studies were randomised control trials; six were phase III trials, one was a phase II trial, and one was a phase II/III trial. Most included studies were international, but there was one trial from each of China and Japan. Six trials recruited younger women aged from mid-teens to 23–26. Two trials recruited older women in mid-twenties and above.

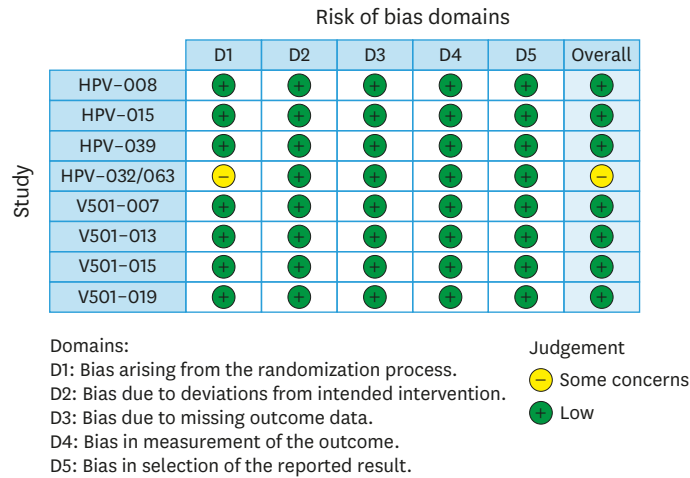
### 2. Risk of bias

Risk of bias was assessed in all 8 trials (Fig. 2). All trials were randomised, double blinded trials with prespecified outcomes. Randomisation sequence was adequately described in all 8 studies. 7 studies adequately described allocation concealment. One study did not adequately

**Table 1.** Included studies

Study name	V501-007	V501-013	V501-015	V501-019	HPV-008	HPV-009	HPV-015	HPV-039	HPV-032/063
Trial number	NCT00365716	NCT00092521	NCT00092534	NCT00090220	NCT00122681	NCT00128661	NCT00294047	NCT00779766	NCT00316693
Year	2000–2004	2001–2007	2002–2007	2004–2009	2005–2010	2005–2012	2006–2012	2008–2014	2009–2013
Phase	III	III	III	III	III	III	III	II/III	II
Intervention	Gardasil	Gardasil	Gardasil	Gardasil	Cervarix	Cervarix	Cervarix	Cervarix	Cervarix
Comparator	Placebo	Placebo	Placebo	Placebo	Hep A vaccine	Hep A vaccine	Placebo	Placebo	Hep A vaccine
Country	International	International	International	International	International	Costa Rica	International	China	Japan
Key inclusion criteria									
Age	16–23	16–23	15–26	24–45	15–25	18–25	≥26	18–25	20–25
Lifetime partners	0–4	0–4	0–4	Any	0–6	Any	Any	NR	NR
Endpoints									
Point prevalence at 4 years							x		
6-mo persistent infection			x	x	x			x	
12-mo persistent infection					x		x	x	x
CIN1+	x	x	x		x		x	x	x
CIN2+	x	x	x		x			x	x
Participants									
Total vaccine	9,087	2,723	6,087	1,910	9,319	3,727	2,877	3,026	375
Total control	9,087	2,732	6,080	1,907	9,325	3,729	2,870	3,025	377
SPDN vaccine	1,298	377	498	496	1,710	986	2,870	286	117
SPDN control	1,319	379	524	505	1,777	980	2,908	270	90

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; NR, not reported; SPDN, seropositive, DNA negative.



**Fig. 2.** Risk of bias plot for studies included in the meta-analysis. HPV, human papillomavirus.

describe allocation concealment, and therefore we had ‘Some Concerns’ about Domain 1 and in the overall assessment. There was one pooled analysis that reported the pooled results of three trials in the SPDN subgroup. This pooled analysis was used for the quantitative synthesis. The overall risk of bias was deemed “Low” in seven trials, and “Some Concerns” in one trial (HPV-032/063).

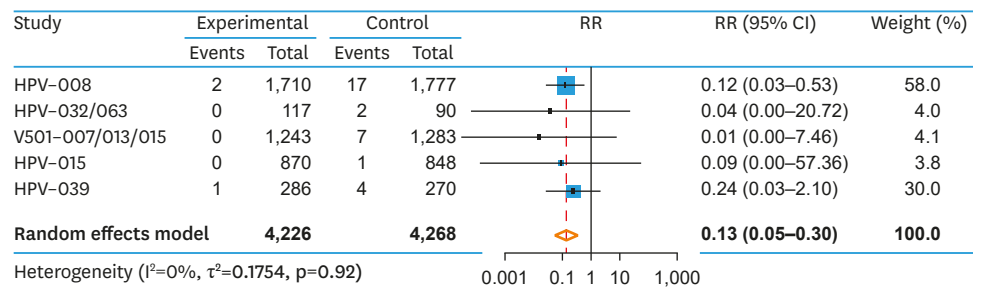
## EFFICACY AMONG SPDN POPULATIONS

### 1. Risk of CIN

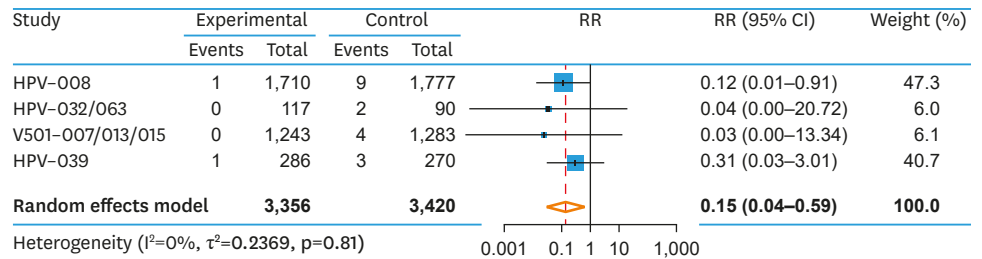
A total of 8 trials, comprising 9,513 SPDN patients (4,732 in the vaccine arm; 4,781 in the placebo arm) reported CIN1+ as an endpoint. One trial (V501-019) with 506 patients in the vaccine arm and 513 patients in the control arm reported no cases of CIN1+, and was therefore not included in the pooled analysis, in line with Cochrane guidelines [31].

### 2. CIN1+

The pooled RR of histologically confirmed CIN1+ was 0.13 (95% CI=0.05–0.30; p=0.003), with a corresponding VE of 87% (95% CI=70%–95%; p=0.003) (Fig. 3). Heterogeneity was low (I<sup>2</sup>=0, p=0.92). A prespecified subgroup analysis found no difference in RR of CIN1+ between the bivalent and quadrivalent HPV vaccine (Q=0.51; p=0.477). The NNV to prevent



**Fig. 3.** Pooled RR of CIN1+ among HPV seropositive, DNA negative women that were prophylactically vaccinated against HPV16/18 versus placebo. CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; RR, relative risk.



**Fig. 4.** Pooled RR of CIN2+ among HPV seropositive, DNA negative women that were prophylactically vaccinated against HPV16/18 versus placebo. CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; RR, relative risk.

one case of CIN1+ was 152 (95% CI=107–256). As there were fewer than 10 studies in this pooled analysis, assessing publication bias was not appropriate [31].

### 3. CIN2+

Six studies, comprising 6,776 SPDN patients (3,356 patients in the vaccine arm; 3,420 patients in the placebo arm), reported CIN2+ as an endpoint. The pooled risk of developing CIN2+ was reduced in the vaccinated versus the unvaccinated group (RR=0.15; 95% CI=0.04–0.59;  $p=0.022$ ), with a corresponding VE of 85% (95% CI=41%–96%,  $p=0.022$ ) (**Fig. 4**). Heterogeneity was low ( $I^2=0\%$ ;  $p=0.81$ ). A prespecified subgroup analysis found no difference in RR of CIN2+ between the bivalent and quadrivalent HPV vaccine ( $Q=0.34$ ,  $p=0.559$ ). The NNV to prevent one case of CIN2+ was 208 (95% CI=135–476). As above, investigation of publication bias was not appropriate [31].

### 4. Risk of persistent infection

#### 6mPI

Four studies reported serotype specific 6mPI, totalling 6,257 SPDN patients (3,097 in the vaccine arm; 3,160 in the control arm). The pooled risk of 6mPI was reduced in the group that received the vaccine (RR=0.22; 95% CI=0.08–0.61;  $p=0.018$ ), with a corresponding VE of 78% (95% CI=39%–92%;  $p=0.018$ ) (**Fig. S1**).

#### 12mPI

Four studies reported serotype specific 12mPI. This included 2,872 patients that received vaccine and 2,877 that received placebo. The pooled RR of 12mPI in the vaccinated versus the unvaccinated group was 0.20 (95% CI=0.05–0.80;  $p=0.035$ ), with a corresponding VE of 80% (95% CI=20%–95%;  $p=0.035$ ) (**Fig. S2**).

### 5. Sensitivity analyses

A prespecified sensitivity analysis was conducted, wherein studies with a high or unclear risk of bias were excluded from the pooled estimate. Excluding these studies, the pooled RR of CIN1+ was 0.14 (95% CI=0.05–0.39;  $p=0.009$ , **Fig. S3**) among vaccinated SPDN women. This was not substantially different to the original pooled result. However, pooled RR of CIN2+, although similar to the original analysis, (RR=0.16; 95% CI=0.02–1.32;  $p=0.065$ , **Fig. S4**), was no longer statistically significant.

In another a priori sensitivity analysis, when a named study was omitted, the pooled estimate remained close to the observed overall estimate. This suggests that no individual study had a large influence on the pooled estimate. The plot for the analysis estimates for CIN1+ and CIN2+ is provided in **Figs. S5** and **S6**.

**Table 2.** Published estimates of HPV vaccine efficacy among SPDN cohorts

Year	Author	Study	Endpoint	Efficacy	95% CI	No. (SPDN)
2009	Olsson et al. [36]	V501-007/FUTURE I/II	HPV-6/11/16/18 related CIN1+	VE 100%	28.7%–100%	2,526
2011	Castellsagué et al. [37]	FUTURE III	HPV6/11/16/18 infection or CIN	VE 66.9%	4.3%–90.6%	1,019
2012	Szarewski et al. [25]	PATRICIA	6mPI	VE 72.3%	53.0%–84.5%	3,421
		PATRICIA	CIN1+	VE 67.2%	10.9%–89.9%	3,487
		PATRICIA	CIN2+	VE 68.8%	–28.3%–95.0%	3,487
2014	Skinner et al. [38]	VIVIANE	HPV16/18 associated 6mPI/CIN1+	VE 86.4%	30.1%–99.0%	NR
2016	Beachler et al. [34]	Costa Rica Vaccine Study	Cervical HPV point prevalence at 4 years	VE 76.5%	54.6%–88.8%	1,384
2018	Arbyn et al. [6]	Future II/PATRICIA	CIN2+	RR 0.19	0.09–0.77	4,506

6mPI, 6-month persistent infection; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; NR, not reported; RR, relative risk; SPDN, seropositive, DNA negative; VE, vaccine efficacy.

## DISCUSSION

This paper represents the first meta-analysis of published data describing L1-based HPV VE among seropositive DNA negative women. We report statistically significant and clinically meaningful efficacy in the prespecified, IARC validated [35] endpoints of (6mPI, 12mPI, CIN1+, and CIN2+). These findings strengthen the case for vaccination of all DNA negative women aged between 15–45, regardless of serostatus, on the basis that DNA negative women must either be seropositive or seronegative, and efficacy among women defined as DNA negative seronegative (such as sexually naive women) has already been conclusively established [6].

Efficacy of L1 vaccination among SPDN women has been described before (Table 2) [6,25,34,36–38]. However, most published estimates either lack statistical power, or use non-standard (or composite) endpoints, which have unclear surrogacy for risk of progression to cervical cancer, thus limiting their clinical utility.

Persistent uncertainty regarding the true lifecycle of HPV [39] means that the mechanism of the observed effect remains unclear. Immunosuppression models both in animals [40,41] and humans [42–47], as well as epidemiological evidence [48–53] support the concept that HPV forms latent infections in basal epithelial stem cells [54,55], and that clinical clearance of HPV infection represents T-cell mediated [39] suppression of the virus to levels below the threshold of detectability: i.e. ‘cryptic, persistent, and reversible infection of cells’ [56], rather than true eradication [54,57,58]. Data regarding immunity following such ‘cleared’ natural infections is inconsistent [50,59–62], but it is likely that natural infection, perhaps particularly among younger women [63], offers a modest degree of protection against type-specific, clinically apparent or DNA-detectable, reinfection [64].

Conceptually, SPDN women may fall into a number of clinically indistinguishable subcategories, across which vaccine efficacy, risk of new infection, and risk of those infections progressing to cytopathological changes, might differ [58]. Assuming a model of latency following initial infection, individual women may be, variously, immune to clinically detectable reinfection or relapse as a result of a competent immune response to the original infection [64]; at risk of exposural reinfection; or at risk of autologous reinfection without re-exposure [65]. It is conceivable that vaccine efficacy might differ between these clinically indistinguishable groups, or indeed that individual women may move between these groups over time during periods of relative immunosuppression [43,44,46,66], as a consequence of changes in the vaginal microbiome [67,68], or as immune responsiveness to HPV infections naturally wanes [69]. These factors may account to some extent for the incomplete efficacy observed in this group as a whole.



It is also unclear why vaccine efficacy should differ so substantially between SPDN women (and indeed among women who have undergone ablative surgical procedures [26,27]) compared to women with detectable DNA infection, among whom vaccination has been demonstrated to be ineffective [6,22–25], but whose classification as DNA positive would, under the supposition of latency, simply reflect an isolated measurement in an infection whose natural history is characterised by oscillation between periods of active viral shedding and periods of latency/immune control [70–72]. One possible answer may be that the immune response observed with L1-based vaccination differs both quantitatively [38], and qualitatively [73], to immune responses occurring as a consequence of natural HPV infection, particularly with respect to the generation of highly-avid neutralising antibodies [73,74]. Such differences may be sufficient to explain the maintenance or prolongation of periods of viral suppression among subjects who have already mounted a competent immune response, or to provide greater protection against HPV infections occurring as a consequence of re-exposure, despite being insufficient to control or reverse active infections.

It should be highlighted that the relative risk and NNV figures presented above should not be understood to represent those of a population-level programme which intended to vaccinate large cohorts of DNA negative women irregardless of serostatus (for example, in the setting of HPV catch-up programs), among whom the efficacy and clinical benefit of vaccination would likely be greater, for a number of reasons which bear mentioning.

Firstly, we do not adjust for the already lower relative risk of infection among our comparator population (SPDN-unvaccinated), relative to the population of all DNA-negative women (reported elsewhere as RR=0.65; 95% CI=0.50–0.80 for HPV-16; RR=0.70; 95% CI=0.43–0.98 for HPV-18 [64]). Secondly, we do not account for the likely composition of any such DNA-negative vaccination cohort, which would comprise not only SPDN women, but also DNA-negative, seronegative women, among whom NNV is substantially lower [6]. Finally, women may also derive benefit from vaccination against vaccine strains with which they have never been infected [75,76], and through cross-protection against non-vaccine serotypes [77–79], although the clinical significance of these benefits are uncertain.

There is ongoing debate [80–83] regarding the cost-effectiveness of population-level HPV catch-up programmes up to age 45, with most models [81–83], excluding those supported by industry [80], concluding that the expansion of population-level vaccination programs to include older women represents inefficient healthcare expenditure and poor value for money. Our findings identify a discrete and increasingly identifiable cohort which may differentially benefit from such programs. Although detailed pharmacoeconomic analysis is beyond the scope of this paper, it is reasonable to expect that approaches which sought to enrich such catchup programs with HrDNA-negative (i.e., “high-efficacy”) cohorts, would result in greater cost-effectiveness through the exclusion of women in whom vaccination has been demonstrated to be ineffective [6,22–25].

### **1. Relevant excluded/missing studies**

A number of studies which examined efficacy among SPDN cohorts could not be included in this metaanalysis. Six potentially relevant studies conducted among women were identified for which no published SPDN data regarding cervical 6mPI, 12mPI, CIN1+ or CIN2+ could be identified: HPV-001 [84], including followup cohorts [85,86], HPV-009 (discussed above), V501-005 [87], V501-027 [88], V501-041 [89], and NCT02296255 [90]. Data describing persistent infection and/or cytopathological endpoints was available for 76.6% of the identified eligible population across

all identified studies (n=51,767/n=67,614). Furthermore, we did not identify any studies or data which failed to corroborate a finding of efficacy among SPDN populations.

## 2. Limitations

This analysis has a number of important limitations.

It is known that HPV infection does not always induce a measurable immune response, and that antibody detectability wanes over time [20,37,91-93]. Negative serological testing does not therefore universally exclude prior infection; this, along with false negative DNA results, and false positive serology results, potentially resulted in the misclassification of some subjects as SPDN in this analysis. This limitation is mitigated by the fact that patients misclassified this way (i.e. classified as Sero-/DNA-, despite being truly Sero+/DNA-), would have been included in the primary ATP analyses of naïve cohorts, among whom efficacy is also well established.

HPV is known to cause infection at anatomical sites not routinely assessed by many of the included studies [4]. The contribution of primary extragenital infections to the prevalence of enrolment seropositivity among study participants could not be determined by this analysis. Similarly, the possibility of protection at extragenital sites afforded by vaccination among SPDN women could not be assessed using available data.

This study analysed vaccine efficacy against HPV16 and HPV18 independently, but did not assess other strains of hrHPV covered by the nonavalent vaccine in widespread clinical use. The single large efficacy RCT of nonavalent vaccine was conducted against a comparator quadrivalent vaccine rather than placebo, which precluded analysis of HPV16/18 outcomes from this trial [30].

Data in this analysis is extracted from RCTs predominantly enrolling women aged between 15–26. Prevalence of SPDN status increases with age [25], and the risk of acquiring new infections (either through reexposure or through relapse of latent infection), as well as the likelihood of such infections progressing to CIN may differ from those among younger women [94-96]. Similarly, the immunogenicity of L1-based vaccines among older women, particularly against HPV18, may differ from that seen among younger women [97].

The above limitations may have implications for pharmaco-economic modelling of the cost-effectiveness of widespread vaccination among SPDN cohorts. Our findings should not be understood to justify population-level vaccination of DNA negative women in the absence of such modelling, which is beyond the scope of this paper.

## CONCLUSION

To our knowledge, this paper represents the first systematic review of published data describing vaccine efficacy among seropositive DNA negative women to date (**Appendix 1**). Notwithstanding the limitations outlined above, we provide strong evidence of the serotype-specific efficacy of HPV L1-based vaccination against validated endpoints of cervical cancer risk, among women previously infected with HPV16/18, including robust efficacy against cervical dysplasia (CIN1+) of 87% (95% CI=70%–95%; p=0.003). These findings are of increasing clinical relevance in the context of a transition towards HPV-based cervical screening [1,2,98,99], and the consequent availability of such results in routine clinical practice. On

an individual level, these results may be of use in the context of shared decision making and individualised risk assessment discussions with HPV16/18 DNA negative women aged up to 45, in accordance with ACIP guidelines[100].

## SUPPLEMENTARY MATERIALS

### Data S1

Supplementary data

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### Data S2

Dataset

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### Fig. S1

Pooled RR of 6-month persistent infection among HPV seropositive, DNA negative women that were prophylactically vaccinated against HPV16/18 versus placebo.

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### Fig. S2

Pooled RR of 12-month persistent infection among HPV seropositive, DNA negative women that were prophylactically vaccinated against HPV16/18 versus placebo.

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### Fig. S3

Bias assessment, CIN 1+ Endpoint.

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### Fig. S4

Bias assessment, CIN 2+ Endpoint.

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### Fig. S5

Analysis Estimate: CIN1+ Endpoint.

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### Fig. S6

Analysis Estimate: CIN2+ Endpoint.

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**Appendix 1. Declarations**

- Title
  - HPV VACCINATION AMONG SEROPOSITIVE, DNA NEGATIVE COHORTS, A SYSTEMATIC REVIEW & META-ANALYSIS
- Authors' contribution
  - Concept and Study Coordination: CME
  - Protocol: CME
  - Literature search and initial writing: CME and RP
  - Data analysis: RP and IP
  - Manuscript writing: CME, RP and DB
  - All authors approved the final manuscript
- Competing interest statement
  - All authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.
- Transparency declaration
  - The authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.
- Ethical approval
  - Ethical approval was not required.
- Details of funding
  - This work received no specific funding.
- Details of the role of the study sponsors
  - This work did not have a sponsor.
- Statement of independence of researchers from funders
  - Not applicable.
- Patient and public involvement statement
  - Patient/public involvement was not sought for this systematic review.
- Trial registration details
  - This review was registered with PROSPERO (CRD42020206888).
- Data sharing statement
  - All data generated or analysed during this study are included in this published article and its supplementary information files.
- Protocol
  - Submitted as a supplementary file .
- PRISMA checklist
  - Submitted as a supplementary file .
- Patient consent
  - Not applicable.

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