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Evaluating the impact of human papillomavirus vaccines

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ABSTRACT

While two prophylactic HPV vaccines have been proven notably efficacious in clinical trials, the effectiveness of these vaccines at the population level remains to be evaluated. To lay the foundation for understanding the strengths and limitations of different endpoints for future effectiveness research, we present a comprehensive review of HPV-related clinical outcomes, including: (i) HPV type-specific positivity and persistence, (ii) Pap diagnoses (ASC-US, LSIL, and HSIL), (iii) histologic cervical cancer precursor lesions (i.e., CIN1, CIN2, and CIN3), (iv) invasive cervical cancer (ICC), (v) anogenital warts, (vi) recurrent respiratory papillomatosis (RRP), and (vii) other HPV-associated cancers (vulvar, vaginal, anal, penile, and oropharyngeal). While research on the vaccines' effects on these HPV clinical outcomes in the general population is presently limited, numerous large trials will soon be completed, making *a priori* discussion of these potential outcomes especially urgent. Furthermore, population level systems to track HPV-associated clinical outcomes may need to be developed for HPV vaccine effectiveness evaluation.
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1. Introduction

1.1. Natural history of cervical cancer

Cervical cancer is a slow-developing disease that is highly preventable if detected early through screening. The early stages of disease, low-grade cervical lesions, are defined by cytology as low-grade squamous intraepithelial lesion (LSIL) and by histology as cervical intraepithelial neoplasia 1 (CIN1). More advanced stages, high-grade cervical lesions, are defined as high-grade squamous intraepithelial lesion (HSIL) by cytology and CIN2/3 by histology, or moderate and severe dysplasia and carcinoma *in situ*. The final stage is invasive cervical cancer (ICC) which is highly preventable by the early detection and eradication of high-grade precancers (HSIL/CIN2/3) [1,2].

Biological changes that lead to ICC typically accumulate over many years. These changes accompany persistent infection with high-risk human papillomavirus (HPV), one of the most common sexually transmitted infections [3,4]. Although extremely common, most HPV infections regress spontaneously [5].

Of over 40 HPV types that infect the female genital tract [3,6], at least 14 are high-risk types that are more likely than other types to increase the risk of subsequent high-grade cervical lesions and ICC [4,7]. High-risk types 16 and 18 are predominant in ICC (~70%) throughout the world [4]. Other high-risk types commonly detected in ICC include HPV 31, 33, 35, 45, 52, and 58 [4] with type-specific positivity rates varying somewhat by country. HPV 6 and 11 may cause benign (non-cancerous) genital warts, and they are occasionally associated with precancerous lesions of the cervix, anus, vulva, and penis [8].

1.2. HPV vaccines

Currently, two HPV prophylactic vaccines have been successfully developed [9–13]. Both are highly efficacious for the prevention of persistent infection with high-risk HPV types 16 and 18 [12]. The quadrivalent HPV vaccine also provides protection against genital warts (condyloma accumunata) associated with low-risk HPV types 6 and 11 [13–15]. This quadrivalent HPV vaccine has been approved and recommended for adolescent females aged 11–12 years, with catch-up vaccination among females aged 13–26 years in the United States. Among women who were currently HPV-DNA-positive in the cervix for types 16 and 18, prophylactic HPV vaccination has been found to have no therapeutic effect against these two HPV vaccine types among women with prevalent HPV 16/18 infections [16]. Thus, L1 virus-like particle-based vaccines are expected to provide maximum benefit to female adolescents who have been given HPV vaccine prior to first sexual intercourse. Because currently available HPV vaccines have not yet been licensed in the United States for males, this present discus-

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sion only addresses the evaluation of the vaccine's impact among women.

Randomized-controlled trials of the efficacy of HPV prophylactic vaccination have presented statistical analyses limited to young females who are considered "naïve cohorts" to HPV vaccine types (i.e., both DNA- and antibody negative to included HPV vaccines types, no previous history of cervical neoplasia or treatment, and with a limited number of sexual partners). Phase IV vaccine effectiveness refers to the impact of the vaccine on HPV infection and associated disease among a more heterogeneous population with varying ages of vaccinated women, vaccine uptake and coverage rates within the population. It is important to highlight the difference between the naïve cohorts who were included in the initial clinical efficacy studies, from a more heterogeneous population (including both the naïve cohort as well as women with prevalent HPV infection and associated disease) who may receive HPV prophylactic vaccination in actual clinical implementation on the population level.

Now that the quadrivalent HPV vaccine is in widespread use in the United States [17] and other countries, it is important to move beyond the existing efficacy trials to determine vaccine effectiveness. Present Phase II/III randomized-controlled trials were designed to measure individual-level efficacy against persistent HPV infection and associated cervical precancers (primarily CIN1 and CIN2) [11,13], but they were not designed to evaluate effects on HPV disease incidence in the general population. Phase IV effectiveness trials are currently ongoing to evaluate the long-term outcomes of the HPV vaccine in the general population.

A better appreciation of effectiveness studies can be gained by discussing two ongoing randomized-controlled trials in Finland. Two individual studies are underway to evaluate the long-term impact of the quadrivalent [18] and bivalent HPV vaccines [19] at the population level. Both studies use the National Finnish Cancer Registry to track the incidence of cervical carcinoma *in situ* (CIS) and ICC as primary endpoints to assess HPV vaccine impact. These effectiveness studies have considerable sample sizes in order to evaluate HPV-associated clinical outcomes on a large scale. For example, a vaccine trial to evaluate the effectiveness of the quadrivalent vaccine plans to recruit a total of 3357 vaccinated adolescent women and 6714 matched non-vaccinated adolescent women [28]. Similar numbers of participants also required by the bivalent vaccine trial for both vaccinated and non-vaccinated arm [29]. Plans are underway to update the Finnish Cancer Registry in order to include data on HPV vaccination status, HPV DNA status, and other HPV-associated clinical outcomes to evaluate HPV vaccine impact after three years for quadrivalent vaccine [18] and after four years for bivalent vaccine trial [19].

2. Potential outcomes for HPV vaccine effectiveness evaluation

Given the data on HPV vaccine efficacy among naïve cohorts in previous clinical trials, it is now necessary to evaluate impact of HPV vaccine on the more heterogeneous general population after the HPV vaccine is available in clinical practice. While we acknowledge that other philosophical and programmatic issues related to HPV vaccine evaluation should be considered by policy makers and medical professionals, understanding each clinical outcome is fundamental to establishing impact of HPV vaccination on the population level.

As summarized in Table 1, potential clinical outcomes for HPV effectiveness evaluation are:

(i) type-specific HPV positivity and HPV persistence,
(ii) Pap diagnoses (ASC-US, LSIL, and HSIL),
(iii) histologic cervical cancer precursor lesions (i.e., CIN1, CIN2, and CIN3),
(iv) Invasive cervical cancer (ICC),
(v) anogenital warts,
(vi) recurrent respiratory papillomatosis (RRP) and
(vii) HPV-associated invasive cancers other than cervical cancer.

For each outcome, we review vaccine efficacy data (Table 2) and appropriateness as an effectiveness indicator.

We focus our discussion on the general population of women regardless of HPV infections whom we refer to as the intention-to-treat (ITT) population. While efficacy trials show HPV prophylactic vaccines prevent persistent infection with HPV 16 or 18 [9,11,12], many of these trials only presented data on women who were not infected with these types (e.g., seronegative and DNA negative to HPV types in HPV vaccines). Although women naïve to HPV infection are more similar to the recommended population to be initially targeted for vaccination (e.g., female adolescents before sexual debut), population-based evaluations will also include women already exposed to vaccine HPV types. We acknowledge that female participants from the ITT population from previous HPV vaccine clinical trials evaluation are likely to be slightly older (18–26 years old) than the full age range for whom the vaccine is currently recommended in many countries. However, ITT analyses may be more likely to model vaccine effectiveness in the general population somewhat more accurately because they include both women who are naïve to HPV types in HPV vaccines, as well as a proportion who have already been previously exposed. Table 2 presents results of clinical efficacy analyses among two group of vaccines.

2.1. Type-specific HPV positivity

2.1.1. Vaccine efficacy

The bivalent HPV 16/18 vaccine prevented acquisition of 89% of all new HPV 16/18 infections and 94% of persistent HPV 16/18 infections over 12 months in ITT analyses [12] (Table 2). Although randomized trials to determine HPV prophylactic vaccine efficacy have also examined persistent HPV infection as a clinical endpoint, the primary endpoint required by the United States FDA for vaccine approval was clinical efficacy against CIN2 or greater. For future HPV vaccine efficacy trials, persistent HPV infection may be worth considering as a surrogate endpoint [20].

2.1.2. Specimen collection

A surveillance system for cervical specimens could *actively* collect samples from women undergoing cytological screening programs or attending STI clinics for the treatment of genital warts. Current guidelines for HPV DNA testing include women over age 30 and those diagnosed with atypical cells of undetermined significance (ASC-US) [21]. Given that these recommendations are relatively recent, however, the extent to which HPV testing is currently ongoing within clinical practice is expected to vary widely. Another approach is to *passively* collect cervical/cervico-vaginal cells already routinely collected during liquid-based cytology screening or stored biopsies obtained from women with abnormal colposcopic findings. However, to evaluate future HPV vaccination impact, linking HPV vaccination status with HPV test results from several different types of HPV-associated clinical outcomes would be ideal. Two methods, Hybrid Capture version 2 (HC2) and polymerase chain reaction (PCR), are commonly used to detect genital HPV DNA. Although the HC2 is the only FDA approved test available in the market, it does not ascertain the presence of individual HPV genotypes. So far, only one standardized type-specific HPV ascertainment method is currently licensed by the FDA for clinical use in the United States. There are a few PCR-based HPV genotyping systems cur-

Table 1
Potential HPV-associated outcomes for vaccine evaluation: advantages and disadvantages.

HPV-associated outcomes	Advantages	Disadvantages
Type-specific HPV positivity (16, 18, 6, 11)	• Type-specific HPV positivity is the direct outcome of current HPV prophylactic vaccines • HPV DNA test is largely independent of interobserver variation • HPV 16/18 infection causes 70% [4] of invasive cervical cancer and changes in HPV 16 and 18 type-specific positivities may represent the most relevant outcomes for long-term HPV vaccine evaluation objectives • The effect of cross-protection for other high-risk types in the long-term will be observed by comparing type-specific distribution in HSIL and ICC to that among women in the general population over time	• Transient infection-HPV DNA test at one point in time does not reflect persistent exposure • Not all HPV infections will lead to the development of high-grade lesions, ICC, or gential warts • No type-specific HPV detection assay is currently licensed for clinical use • Sensitivities differ for the type-specific results among DNA tests Sensitivities differ between the specimen collection methods (e.g., physician-collected versus self-collected sample)
Persistent HPV type-specific HPV (16, 18, 6, 11)	• Persistent HPV is a sensitive predictor of high-grade cervical lesions and invasive cervical cancer	• No clear definition of persistent HPV infection • Cost for repeating DNA tests for persistent HPV infection in a large population
LSIL (cytology)/CIN1 (histology)	• As LSIL/CIN1 is more common, more feasible to compare the number of lesions reduced among vaccines within a relatively short time • Proven efficacy against CIN1 related to vaccine types	• High potential for regression • Vaccine types HPV 16/18 only account for less than 25% of LSIL [31] • Characteristic of multiple HPV infections • Interobserver variability in the interpretation of cytology and histology • LSIL prevalence is also affected by changes in the screening guidelines.
HSIL (cytology)/CIN2/3 (histology)	• Better proxy for ICC than LSIL/CIN1 • Higher potential for invasion • Larger proportion (∼50%) of HSIL/CIN2/3 positive for HPV 16/18 [4] • Proven efficacy against HSIL/CIN2/ CIN3 related to vaccine types	• Interobserver variability in cytology and histology interpretations • Similar to LSIL/CIN1. HPV prevalence is affected by the screening guideline • Only ∼50% HSIL positive for vaccine HPV 16/18 [4]
Invasive cervical cancer (ICC)	• Outcome associated with mortality • HPV type-specific distribution differ between HSIL and invasive cancer • No proved vaccine efficacy yet against ICC	• Long follow-up time for incident case detection given the rare incidence of ICC • Most precancers will be removed or treated by the screening before they progress to invasive cancer
Anogenital warts	• Common and often symptomatic HPV-associated disease • Proven efficacy against most genital warts related to vaccine types 6/11	• Only quadrivalent vaccine provide protection against genital warts
Recurrent respiratory papillmatosis (RRP)	• HPV 6 and 11 are central cause of recurrent respiratory papillmatosis	• RRP is rare and it is not easy to observe the reduction in incidence rate • No data available for women aged in recommended vaccination • Only quadrivalent vaccine provide protection against genital warts
Other HPV-associated cancers (vulvar, vaginal, anal, penile, and oropharyngeal)	• High-risk HPV types 16 and 18 are common causes	• A proportion of HPV-associated cancers are not attributed to HPV infection • Those cancers are generally relatively rare clinical outcomes

Table 2
HPV Vaccine efficacy in intention-to-treat analyses by HPV infection, cervical abnormalities, and genital warts.

Vaccine type	Endpoint	Efficacy in the naive population	Efficacy in intention-to-treat analyses (ITT)
Quadrivalent vaccine	Incident infection related to HPV 16/18	(data not available)	(data not available)
	Persistent infection related to HPV 16/18 for 12-month follow-up	(data not available)	(data not available)
	Cervical lesions related to HPV 16/18 [9]		
	CIN1	(data not available)	(data not available)
	CIN2	100% (95% CI: 86–100)	57% (95% CI: 38–71)
	CIN3	97% (95% CI: 79-100)	45% (95% CI: 23–61)
	Cervical lesions related to HPV 16/18/6/11 [15]		
	CIN1	100% (95% CI: 92–100)	62% (95% CI: 46–74)
	CIN2	100% (95% CI: 81–100)	30% (95% CI: <0–56)
	CIN3	100% (95% CI: 76–100)	12% (95% CI: <0–44)
	Cervical lesions, irrespective of HPV type [15]		
	CIN1	(data not available)	25% (95% CI: 12–36)
	CIN2	(data not available)	13% (95% CI: <−34)
	CIN3	(data not available)	−9% (95% CI: <0–22)
	Anogenital warts and external lesions related to HPV 16/18/6/11 [15]	100% (95% CI: 94–100)	73% (95% CI: 58–83)
	Condyloma	100% (95% CI: 92–100)	76% (95% CI: 61–86)
	VIN2/3 or VAIN2/3	100% (95% CI: 49–100)	62% (95% CI: <0–89)
	Anogenital warts and external lesions related to any HPV type [15]	(data not available)	34% (95% CI: 15–49)
	Condyloma	(data not available)	51% (95% CI: 32–65)
	VIN2/3 or VAIN2/3	(data not available)	26% (95% CI: <0–63)
Bivalent vaccine	Incident infection related to HPV 16/18 [12]	95% (95% CI: 84–99)	89% (95% CI: 77–95)
	Persistent infection related to HPV 16/18 for 12-month follow-up [12]	100% (95% CI: 52–100)	94% (95% CI: 61–100)
	Cervical lesions related to HPV 16/18		
	CIN1+	100% (95% CI: 42–100)	(data not available)
	CIN2+	100% (95% CI: −8–100)	(data not available)
	Cervical lesions, irrespective of HPV type		
	CIN1+	(data not available)	(data not available)
	CIN2+	(data not available)	(data not available)

rently in commercial development or commercially available. The reproducibility and high sensitivity and specificity of broad spectrum HPV genotyping prototype assays have been well documented in a variety of sample types including liquid-based cytology media, paraffin-embedded tissues and other transport media.

2.1.3. Advantages and disadvantages

One advantage of measuring HPV 16, 18, 6, and 11 infections as an outcome is that they are direct targets of current HPV prophylactic vaccines. HPV type-specific prevalence may potentially provide a more sensitive indicator of vaccine impact than either cytological or histological outcomes of precancerous cervical lesions and ICC [22–24]. Unlike the relatively high potential for inter-observer variation of cytological and histological interpretation, HPV DNA testing results are generally less observer-dependent [25].

Changes in HPV 16 and 18 type-specific prevalence may be the most relevant to long-term HPV vaccine evaluation outcomes because those types account for ∼70% of ICC and ∼50% of high-grade cervical precancer cases [4]. Moreover, both clinical outcomes of ICC and HSIL/CIN2/3 may change over time due to potential change in cervical cancer screening practices. Comparisons of HPV type distribution in women with normal and abnormal cervical disease over time will allow the evaluation of the potential effect of HPV prophylactic cross-protection. The potential for current HPV 16/18 vaccine formulations to provide cross-protection against infections caused by non-vaccine HPV types has been reported [26], but the clinical relevance of such protection is not yet understood. The detection of type-specific HPV prevalence circulating in populations will also be critical to evaluate potential HPV type replacement versus potential unmasking of commonly occurring HPV co-infections. If type-specific HPV prevalence is to be determined, the timing of collection of the DNA material is critical. Ascertaining type-specific HPV prevalence among representative samples of women before widespread vaccination will allow tracking of population level changes in type-specific HPV prevalence over time.

Although persistent HPV infections are associated with a higher risk of high-grade cervical neoplasia and ICC [27], a clear definition of persistent infection has not yet been identified. It is also important to acknowledge that the sensitivity of type-specific HPV detection varies by collection method. Compared to self-collected vaginal samples, physician-collected specimens have been to shown to have a higher sensitivity for the detection HPV infection (86.2% versus 98.3%, respectively) [28]. HPV vaccine evaluation programs, whether incorporating either a single time point or repeat HPV DNA testing, might prove to be relatively costly in large populations [29] unless HPV testing results are obtained as a result of clinical care.

While HPV infection is an important evaluation outcome, a number of additional factors should be considered. First, regardless of HPV types, most cervical HPV infections will be cleared within 1–2 years without treatment [5]. Observed reductions in the incidence of HPV infection might not necessarily correlate with decreases in high-grade lesions and ICC cases because only a portion of women with HPV infection will develop high-grade lesions and ICC.

2.2. Low-grade cervical lesions (LSIL/CIN1)

2.2.1. Vaccine efficacy

The quadrivalent vaccine prevented 62% of CIN1 associated with four vaccine HPV types among all subjects in a large Phase III study

[15] (Table 2). Compared to CIN1 caused only by vaccine types, vaccine efficacy was lower (25%, 95% CI: 12–36%) for CIN1 caused by any HPV types [15].

2.2.2. Advantages and disadvantages

LSIL/CIN1 is relatively common and develops more quickly than HSIL/CIN2/3 or ICC. About 1.5 million women are diagnosed with low-grade lesions each year in the United States [30]. Thus, due to larger sample sizes, changes in the incidence of low-grade lesions should be relatively easier to ascertain on the population level than high-grade lesions or ICC that are relatively rare and take longer to develop. Because most low-grade cervical lesion cases regress spontaneously, however, low-grade lesions are an insensitive indicator for ICC [5]. Although vaccine efficacy against vaccine-type CIN1 has been demonstrated in clinical trials, HPV 16 and 18 are generally found in a smaller proportion (approximately a quarter) of all CIN1 cases, in comparison with approximately 70% among ICC and CIN2/3 cases [4,31]. Since multiple HPV types have been identified in a large proportion of low-grade cervical lesions [31,32], it is also unclear which HPV type(s) is casually attributable to the lesion. Another issue is the reproducibility of histology (CIN1) and cytology (LSIL) interpretations of low-grade lesions. Both cytology- and histology-based diagnoses are subject to interpretations that vary markedly among laboratories. This variation is particularly notable for CIN1 [33]. Cytological diagnoses of LSIL have been shown to be more reproducible (68%) than that of histologically confirmed CIN1 (43%) [33]. Thus, HPV typing data for LSIL cases can be considered for HPV vaccine evaluation efforts, particularly given the relatively large number of LSIL cases diagnosed on a population based level.

Changes in the guidelines for cervical cancer screening may also affect the incidence of LSIL/CIN1, confounding reductions in disease caused by the HPV vaccine. Therefore, using trends in LSIL/CIN1 alone without data on individual HPV types or without accompanying data on HPV 16 and/or 18 in HSIL/CIN2/3 may not be a useful approach for HPV vaccination evaluation. Further, all efforts for HPV vaccine evaluation would benefit from accompanying data on HPV vaccination history.

2.3. High-grade cervical lesions (HSIL/CIN2/3)

2.3.1. Vaccine efficacy

Available ITT data on the quadrivalent vaccine showed a reduction of 57% of CIN2 and 45% of CIN3 related to HPV 16 or 18 among vaccine recipients relative to placebo recipients [9]. However, HPV vaccine efficacy was lower when the analysis included all CIN2/3 regardless of HPV type. Efficacy associated with the prevention of CIN2 due to any HPV type was 13% (95% CI: <0–34) and for CIN3 was −9% (95% CI: <0–22) [9]. These findings indicate that vaccine efficacy is largely limited to high-grade lesions only caused by vaccine types, rather than lesions related to non-vaccine types.

2.3.2. Advantages and disadvantages

HSIL/CIN2/3 are stronger surrogate outcomes for invasive cervical cancer than CIN1 because of their higher potential to progress to invasive cancer [5,32]. Given that approximately 50% of CIN2/3 are positive for HPV types 16 or 18 [4], a similar proportion of CIN2/3 cases may potentially be prevented by vaccination [9].

Despite the quadrivalent vaccine's 50% efficacy against CIN2/3 related to HPV 16 or 18 in ITT analyses, several questions remain. First, the extent to which both HPV prophylactic vaccines will effectively reduce CIN3 in the general population is based on relatively small sample sizes. In quadrivalent vaccine trials due to a relatively limited sample size, the incidence of CIN3 (irrespective of HPV types) in vaccinated women was close to that of non-vaccinated women (0.7 versus 0.9 per 100 persons, respectively) [9]. Vaccine efficacy against high-grade lesions (CIN2/3) was largely attributed to a significant reduction in CIN2 incidence [9,34]. Second, as compared with CIN1, a large quality control study within the United States showed a relatively higher concordance of CIN2 or greater diagnoses by histology (77%). This is somewhat different from the reproducibility of HSIL diagnoses by cytology which was reported as being under 50% [33]. A potential concern of both high-grade cervical cytology and pathology interpretation is the substantial variation in readings observed across laboratories [33]. Thus, for the accurate determination of cervical precancer, centralized cytological and pathological adjutification, or more specific molecular markers for these lesions, should be developed to improve capacity for vaccine evaluation. Third, similar to clinical outcomes of LSIL/CIN1, efforts to evaluate HPV vaccine effectiveness for HSIL/CIN2/3 may be difficult due to the ongoing changes in cervical cancer screening programs overtime. Finally, because only half of HSIL/CIN2/3 cases are attributable to vaccine types, vaccine effectiveness might not be salient unless type-specific HPV DNA testing results are taken into account. To compare HPV type distribution in lesions among vaccinated and unvaccinated cases would benefit from obtaining vaccine history on all reported cases, for example, by linking data from the registry for HPV-associated clinical outcomes to an established vaccine registry. Ongoing assessment of cervical cancer screening rates will also be required in order to evaluate the burden of CIN2/3 over time.

2.4. Invasive cervical cancer

ICC has not yet been a reported outcome of Phase II/III efficacy studies. Due to the long time period for ICC development, as well as the need to treat cervical precancerous lesions, HSIL/CIN2/3 is usually considered an appropriate surrogate endpoint for ICC for the evaluation of HPV vaccine efficacy. However, since a proportion of high-grade lesions ultimately regress and ICC is the ultimate cause of mortality, whether or not HPV vaccines would definitively reduce the incidence of ICC within the population over a longer term remains unknown.

2.4.1. Advantages and disadvantages

A major disadvantage of using ICC as an outcome of future effectiveness evaluation is that few women with cervical precancer will develop invasive cancer [5,35]. Consequently, low statistical power that results from the low incidence and long duration of the development of ICC make the following up of ICC as an endpoint for vaccine evaluation difficult. Moreover, assessing ICC is challenging because most cervical precancers are detected and treated at the early stage by screening, limiting the ability to evaluate the effectiveness of HPV vaccine in preventing ICC. In the developed countries, it will take an estimated 30 years to observe a reduction of 20% in cervical cancer incidence within the population of 75% HPV vaccination rate [36].

2.5. Anogenital warts

2.5.1. Vaccine efficacy

In ITT analysis, the quadrivalent HPV vaccine has been shown to reduce 73% of external genital lesions related to vaccine HPV types 16, 18, 6 and 11 [10].

2.5.2. Advantages and disadvantages

Low-risk types HPV 6 and 11 account for the majority of anogenital warts cases [8,37,38]. Approximately 1.4 million people have genital warts in the United States [8], with the highest incidence and prevalence rates among women 25–34 years old [39]. Although

anogenital warts are usually benign and not associated with cancer risk, they may be a good endpoint to monitor HPV vaccine effectiveness because they take less time to develop than most HPV-related cancers and the majority are symptomatic, and thus more likely to be detected. However, most genital warts are not diagnosed by histology and thus tissues are not routinely available.

Based on data on the quadrivalent HPV vaccine, the ITT population in current clinical trials includes women relatively older than 18 years, but no data are available for those who are less than 18. Moreover, only the quadrivalent HPV vaccine is protective against HPV 6 and 11. As a result, the reduction through HPV vaccination might not be clearly ascertainable if two different vaccines, only one of which includes protection against anogenital warts, are available on the market.

2.6. Recurrent respiratory papillmatosis (RRP)

2.6.1. Vaccine efficacy

There is no proven efficacy on RRP at the present time.

2.6.2. Advantages and disadvantages

As with anogenital warts, low-risk types HPV 6 and 11 account for the majority of RRP cases [8,37,38]. RRP is a rare disease with the incidence is estimated to be 3.5 per 100,000 each year [40].

To examine the vaccine impact on RRP may be challenging given that RRP is rare. Currently, no efficacy data is available for younger women in the recommended vaccination age. Using RRP as a study outcome is subject to the same concerns discussed for anogenital warts, namely potential difficulties in HPV vaccine evaluation caused by two HPV vaccines in the market, only one of which prevents the HPV types that cause RRP.

2.7. Other HPV-related cancers (anal, oropharyngeal, penile, vaginal, and vulvar)

2.7.1. Vaccine efficacy

In the ITT population, vaccine efficacy against high-grade vulvar and vaginal lesions related to HPV 16 or 18 was 71% for the quadrivalent vaccine [41]. For the prevention of lesions due to all vaccine types, a slightly lower efficacy of 62% was observed [15].

2.7.2. Advantages and disadvantages

High-risk HPV types are important etiological agents for vulvar, vaginal, anal, penile, and oropharyngeal cancers [42]. Estimates of HPV prevalence of anal cancer are about 71% [43]. Approximately 59% of vaginal cancers and 36% of vulvar cancers have been found to be HPV-DNA-positive [44], comparable to an overall HPV prevalence of 48% in penile cancer cases [45] and 36% in oropharyngeal cancers [46]. Since many of these cancers have a notable proportion of cases that are not attributable to HPV infection, the implementation of HPV vaccine evaluation based on these cancer outcomes may not be as straightforward.

Because HPV 16 and 18 are the most common types in these other HPV-associated cancers, the HPV vaccine has great potential for cancer prevention. However, given that certain cancers including vaginal and vulvar cancers are generally rare among women within the population, using these endpoints to evaluate the HPV vaccines may not be practicable.

2.8. The effect of cross-protection and type replacement

As mentioned earlier, the effect of cross-protection should also be considered for vaccine evaluation. While HPV vaccination effectively prevents infection with HPV 16 and 18 and related cervical lesions, HPV vaccination may provide protection against other types genetically similar to vaccine types. Preliminary data suggest that the bivalent vaccine study has demonstrated an efficacy for HPV 31 and 45, albeit lower than that for HPV 16 and 18 [26]. However, the biological mechanisms of different HPV types are not yet fully understood, and the significance of cross-protection is limited by a small number of lesions, short study period, and lack of data on ICC. It is worth noting that following HPV vaccine implementation, other high-risk HPV types than HPV 16 and 18 could replace the biological niche of HPV 16 and 18, thereby causing a relatively greater proportion of cervical cancer and cervical cancer precursors cases [9,10]. If this occurs, there is a potential to offset the benefits of vaccination. HPV vaccination evaluation programs should consider this possibility and evaluate changes in HPV type distribution in high-grade lesions and ICC over time relative to HPV types found in the general population with documentation of HPV vaccination history. Long-term follow-up during further vaccine evaluation is expected to address those two issues.

2.9. Summary

Each of the proposed outcomes has its own strengths and limitations, making none clearly preferable for all applications. Because HPV vaccine effectiveness evaluation will heavily rely on data from large population-based studies, programmatic processes for data collection are also important. For example, a well-established vaccine registry is highly desirable to estimate the potential immunity and vaccine efficacy of varying dosing schedules. Ideally such a vaccine registry would contain enough information to allow linkage to a wide array of HPV-associated clinical outcomes. To monitor the changes in these clinical outcomes over time, a central reporting system at the state-level could ideally be established to collect information for the whole population.

3. Recommendation for including HPV, histology or cytology outcomes in statewide reporting systems

We now apply these principles to statewide reporting systems. We use the example of North Carolina, a state with ICC incidence higher than the rest of the United States (9.4 versus 7.7 women per 100,000) [47] and far short of the Healthy People 2010 goals [48]. Currently, the quadrivalent HPV vaccine has been introduced to girls and women age between 11 and 26 years in North Carolina. Given the significant disease burden of cervical cancer and availability of the HPV vaccine, adding relevant HPV-associated outcomes to appropriate registries will facilitate a better understanding of the impact of HPV vaccine in North Carolina. To the best of our knowledge, only invasive cervical cancer, high-grade vulvar and vaginal lesions (VIN3 and VAIN3), and anal intraepithelial neoplasia (AIN) are identified as reportable in North Carolina. However, many outcomes that are potentially important to vaccine evaluation are not being monitored at this time. These include HPV DNA testing results, low-grade and high-grade cervical lesions confirmed by cytology and histology, anogenital warts, recurrent respiratory papillomatosis, and other HPV-associated cancers discussed above.

To include HPV-associated outcomes in a statewide registry, several points would need to be considered. First, there is an existing central cancer registry in North Carolina to record and compile all diagnosed invasive cancer cases across North Carolina for the purpose of monitoring the incidence and mortality. Due to the long duration of invasive cancer development, it will take decades to observe changes in cancer incidence. The establishment of infectious disease reporting system including other HPV-related outcomes will be essential to evaluate the long-term impact of HPV vaccine. A revised administrative code could be enacted to identify HPV-associated outcomes as reportable and require all laboratories licensed in North Carolina to report HPV-associated outcomes

through a new reporting system. For example, HPV-associated outcomes could be identified by the North Carolina Department of Health. The relevant linkage of these HPV-associated outcomes to systematic database on vaccination history, and ideally cytological screening history could be established for comprehensive HPV vaccine evaluation.

Although HPV vaccine status may be desirable for vaccine evaluation, most vaccine registries in the United States are not complete even in the pediatric populations where the majority of vaccines are delivered. Notable barriers to comprehensive and required vaccine registration make it improbable to systematically document vaccine status in most states. Other practitioners (e.g., family practitioners, OB/GYNs, and pediatricians) provide HPV vaccination, and they are often not actively engaged in routine vaccine registration. Thus, implementation of required HPV vaccine registration is not likely to be available soon in the absence of legislative requirements. Therefore, it will be difficult to designate those who have truly not been vaccinated. Within a year after Advisory Committee for Immunization Practices (ACIP) recommended HPV vaccine for female adolescents, HPV vaccine coverage had reached approximately 25% coverage of females aged 13–17 years in United States [49]. We acknowledge that although the vaccine registration at the population level is desirable, linkage to vaccination status should not be considered a requisite to estimating population impact of HPV vaccines. Rather it would represent a bonus in evaluating several endpoints including potential waning immunity and efficacy of variable dosing schedules. This applies not only to HPV vaccine registration systems, but also to the registration of other vaccines.

Several programmatic issues might arise when working to incorporate HPV-associated outcomes to the list of reportable conditions at the state-level. Adding existing cytology and pathology laboratories to the reporting network requires time, financial support, and effort. There is also a need to establish reporting systems for each laboratory and to consolidate the duplicate reports from different laboratories. Taken together, these additional processes for the new reports are expected to increase associated administrative costs. Because the terminologies used for cytology and histology differ, data should be reported separately from laboratories for cytology and histology outcomes. Given that the current cytology or pathology database from laboratories are also not systematic, data management software could be customized to build transmission capability across different catchment sites. Wide and representative population sampling would also be critical. If these issues are successfully addressed, the reporting system will be strengthened to include additional HPV-associated clinical outcomes beyond the traditional reporting of ICC only. The additions would represent a critical step in establishing an effective system for future HPV vaccine evaluation on the state-level.

4. Conclusion

HPV vaccines offer a unique opportunity to reduce the burden of cervical cancer and associated outcomes at the population level. The full extent of the usefulness of HPV vaccination for reducing HPV-associated morbidity and mortality, however, would benefit from the design and implementation of reporting systems capable of gathering data for HPV-associated endpoints. We identified potential HPV-associated outcomes that are relevant for assessing effectiveness as well as specific administrative actions that can facilitate the process of determining the effectiveness of HPV vaccine at the population level. A few states in the United States have initiated reporting systems to enable appropriate HPV vaccine evaluation. New Mexico has established a laboratory-based reporting system to collect Papanicolaou test, cervical pathology, and HPV testing results on the state-level. Florida requires comprehensive reporting of all abnormal cervical cytology and histology, high-risk HPV infections, respiratory papillomatosis (age 0–6 years), and anogenital HPV in children less than 12 years of age through a statewide electronic reporting system. Connecticut has required the reporting diagnosis of CIN2/3 and adenocarcinoma-*in situ* (AIS). Reporting systems for HPV-associated outcomes may be possible in North Carolina and many other states.

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