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Intention-to-prevent analyses for estimating human papillomavirus vaccine efficacy in clinical studies

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ABSTRACT

HPV vaccine efficacy trials have been conducted in populations exposed to HPV infection (i.e., sexually active individuals); participants were not excluded from participating in the trials based on their HPV status at baseline. Thus, some participants could have been infected at baseline with 1 or more vaccine HPV types. Because HPV vaccines are prophylactic and do not affect existing HPV infections, prophylactic efficacy was assessed in a per-protocol population (those not infected at enrollment to the HPV type being analyzed who also completed the 3-dose regimen of vaccine and had no protocol violations). Supportive intention-to-treat (ITT) and modified ITT, were also conducted to include those with prevalent HPV infection. ITT analyses included those who received ≥1 dose of vaccine and had efficacy follow-up regardless of whether or not they were infected with HPV prior to vaccination. Efficacy in the ITT population simply reflects the amount of prevalent infection in a particular population of study subjects. Intention-to-prevent (ITP) analyses included those who received one dose of vaccine, had efficacy follow-up, and were not infected at enrollment to the HPV type being analyzed.

While all of these analyses have been presented, there has been little discussion regarding their respective significance. In this methodological review, we show that an ITT analysis does not preserve an unbiased comparison of treatment groups in relation to estimating prophylactic HPV vaccine efficacy. Furthermore, ITP is more suitable at preserving an unbiased comparison of treatment groups in relation to estimating prophylactic HPV vaccine efficacy.

1. Introduction

Human papillomavirus (HPV) causes nearly all cervical cancer cases, as well as substantial proportions of anal, vulvar, vaginal, penile and oropharyngeal cancers [1]. The licensed quadrivalent HPV 6/11/16/18 (4vHPV) vaccine and bivalent HPV16/18 (2vHPV) vaccine address oncogenic HPV types 16 and 18 that cause approximately 70% of cervical cancer cases worldwide [2]. The licensed nine-valent HPV (9vHPV) vaccine addresses the oncogenic HPV types 16/18/31/33/45/52/58 which cause approximately 90% of cervical cancer cases worldwide [3–5].

The clinical trials evaluated HPV vaccine efficacy by using pre-cancerous lesions as the primary efficacy surrogate endpoints for invasive cervical cancer. Such clinical trials were conducted on sexually active individuals 16–26 years of age who were at-risk for becoming infected with HPV and developing pre-cancerous cervical lesions. The time from acquisition of infection to the development of precancerous lesions (e.g., cervical intraepithelial neoplasia grade 2 or worse, which is the obligate precursor of cervical cancer) can take up to 90 months [6]. Moreover, the standard of care is to screen for and excise pre-cancerous lesions to prevent invasion.

The licensed prophylactic HPV vaccines consist of virus-like particles (VLPs) composed of the viral capsid protein L1 of each HPV type in the vaccines. These vaccines were expected and confirmed to be strictly prophylactic in nature [5,7–10]. To demonstrate prophylactic HPV vaccine efficacy, the definitive clinical trials could have screened and recruited only women who were uninfected at baseline; however, this approach would have produced a highly selected population with unknown biases that would not represent the population in which the vaccine would be subsequently used. Additionally, if only individuals without HPV infection were eligible for the pivotal efficacy trials, HPV vaccines would likely be indicated only in individuals who are HPV-negative, which would make vaccination programs infeasible for sexually active individuals.

Approximately 60% of sexually active persons will become infected with HPV during their lifetime, thus many enrolled in HPV vaccine efficacy clinical trials could already be infected with one or more of the HPV types that the vaccine is designed to protect against, or with HPV

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types that are not in the vaccines [11,12]. However, infection with all HPV types in each of the 3 HPV vaccines is rare. For instance, infection with all four types present in the 4vHPV vaccine is 0.1% of 3578 women enrolled in North America by serology or HPV DNA [13], and none were infected with all nine HPV types in 9vHPV vaccine, so essentially all subjects vaccinated with 2vHPV, 4vHPV or 9vHPV vaccines would potentially derive some benefit by being vaccinated [14,15].

Intention-to-treat analysis is frequently viewed as a mainstay of unbiased analysis of randomized clinical trials because its basic premise is to preserve the unbiased comparability of treatment groups with respect to estimation and subsequent inference relating to treatment effect. It is commonly accepted that sub-dividing study populations into analysis cohorts benefits the modality under study, and that an ITT analysis provides a more valid estimate of overall efficacy. In the context of HPV vaccination, however, estimation of overall efficacy via an ITT approach without critical assessment of what 'overall' means leads to inappropriate conclusions because such prophylactic vaccines make no claim for a therapeutic effect and, in fact, have demonstrated no therapeutic effect [5,7–10].

This article discusses the limitations of ITT analyses in the context of efficacy trials of prophylactic HPV vaccines and proposes that an alternative intention-to-prevent (ITP) analysis should be preferred.

2. Methods and results

2.1. Limitations of ITT analyses in HPV vaccine clinical trials

2.1.1. Assessment of vaccine efficacy in different analysis populations

By way of explanation, the metric called vaccine efficacy is a percent risk reduction, calculated as 100% x (1 minus the relative risk). In HPV vaccine clinical trials, relative risk is typically calculated as the risk of disease in the "innovator vaccine group" divided by the risk of disease in the "control group". The control group can be a placebo group or an existing standard-of-care vaccine. Risk of disease can be an incidence rate, or count of disease cases if the innovator vaccine group and the control group have approximately equal follow-up times. Thus, the vaccine efficacy metric is the percent reduction in the control group risk of disease that the innovator vaccine can generate.

In HPV vaccine clinical trials, vaccine efficacy against HPV types covered by a particular HPV vaccine was evaluated on an HPV-type-specific manner and conducted by identifying individuals in the sexually active efficacy population who are not infected at baseline with the vaccine-HPV type being analyzed, remain uninfected through the vaccination series, and receive the appropriate 3 doses of the vaccine without protocol violations. Such individuals approximate HPV-uninfected pre-adolescents for that particular vaccine-HPV type, but are actually at risk of acquiring infection and disease and therefore represent a suitable population to evaluate the efficacy of the HPV vaccine for that particular HPV type. Efficacy calculated in this population (termed the per-protocol efficacy [PPE] or according-to-protocol [ATP] population in vaccine efficacy trials) is interpretable as prophylactic HPV vaccine efficacy. It has been consistently shown in clinical trials that prophylactic HPV vaccine efficacy approached 100% for HPV types covered by a particular HPV vaccine [5,8,9,16].

Conversely, efficacy against a particular vaccine-HPV type that is calculated in a population of individuals who are HPV-infected for that particular type during the vaccination period is interpretable as therapeutic efficacy (i.e., a measure of whether the vaccine can clear existing infection). In HPV VLP vaccine clinical trials, no therapeutic efficacy has been demonstrated [5,7–10].

To illustrate this point, analysis populations previously used in efficacy trials of the 4vHPV vaccine are shown in Table 1; these include the PPE and ITT populations as well as the ITP population, a modified ITT population that includes only subjects not HPV-infected prior to vaccination [8,9,17]. An example of efficacy analysis of 4vHPV vaccine to prevent the endpoint of CIN2+ associated with HPV type 16 or 18 based on these 3 analysis populations in the Female United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) II study is shown in Table 2 [8]. The estimated vaccine efficacy in the prophylactic analysis populations (PPE, ITP) is substantially higher than in the ITT population because the incidence of the efficacy endpoint in the 4vHPV vaccine group is much higher in the ITT population than in the PPE and ITP population. As noted, subjects who were infected prior to vaccination are included in the ITT population and excluded from the ITP population. Thus, most reports of disease in the ITT population came from subjects who were infected prior to vaccination.

2.1.2. Impact of prevalence of baseline HPV infection on the estimate of vaccine efficacy in the ITT population

Since HPV VLP vaccines are prophylactic but not therapeutic vaccines, HPV-related disease prevention is expected among those not HPV-infected but not expected among those HPV-infected during the vaccination period. In statistical analysis parlance, existing HPV infection status (infected versus not-infected) at the time of vaccination is a clearly established subject characteristic that has an interaction with vaccine efficacy. Given that the ITT analysis population includes both HPV-infected and not HPV-infected at the time of vaccination, the estimate of HPV vaccine efficacy in an ITT analysis population, which is commonly interpreted as a measure of 'overall' vaccine efficacy, is in reality a mixture of prophylactic and 'therapeutic' efficacy. In fact, there is no therapeutic efficacy and none is claimed, so any prevalent infection or disease simply dilutes the true prophylactic efficacy and does not contribute to the understanding of the effectiveness of the vaccine. Efficacy in the ITT population simply reflects the amount of prevalent infection in a particular population of study subjects. Another interesting observation is that when vaccine is used in 11-year-old children, the ITP and ITT analysis are equivalent because of the absence of prevalent infection or disease in this population. This is why the ITP analysis is vital to the efficacy metric because in sexually active individuals, where efficacy can be measured, the ITP population best approximates the situation expected in uninfected young adolescents. In contrast, the measure of overall vaccine efficacy calculated in the ITT analysis population via a 'pooled' analysis (i.e., without regard to adjustment for HPV infection status when there is a clear interaction between HPV infection status and vaccine efficacy) has no meaningful and practical interpretation and is not an appropriate statistical analysis approach.

On the other hand, one might argue that the appropriate solution to the problem of prevalent infection is to recruit study subjects who are not infected with the HPV types under study. Such pre-screening is impractical for several reasons. Studying the safety of the vaccine administered to subjects who are prevalently infected is an important question that requires study in the clinical trials, as well as to demonstrate efficacy against HPV types to which study participants were not infected. Additionally, developing an HPV vaccine that requires pre-screening for HPV infection would render any vaccination program in a general population infeasible. The clinical development program of such a vaccine is designed to demonstrate prophylactic efficacy and safety on an HPV type-specific basis and support the development of a vaccine suitable for a real-world vaccination program. It should not be designed to specifically recruit a study population for a clinical trial because it creates a favorable ITT analysis.

Additionally, in HPV vaccine efficacy clinical trials where a primary efficacy endpoint such as incidence of high-grade cervical disease (CIN2+) takes several years to develop and be observed, the characteristic of being HPV-infected at baseline is magnified over the duration of a clinical trial because it is just such a characteristic that contributes to the development of CIN2+ over the course of a clinical trial, and ultimately contributes to accumulation of the primary efficacy endpoint. This type of impact in HPV vaccine efficacy trial, where subgroups in an ITT population who have no expected benefit from therapy yet actually contribute to increasing the count of primary