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# Optimal control with multiple human papillomavirus vaccines

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ABSTRACT

A two-sex, deterministic ordinary differential equations model for human papillomavirus (HPV) is constructed and analyzed for optimal control strategies in a vaccination program administering three types of vaccines in the female population: a bivalent vaccine that targets two HPV types and provides longer duration of protection and cross-protection against some non-target types, a quadrivalent vaccine which targets an additional two HPV types, and a nonavalent vaccine which targets nine HPV types (including those covered by the quadrivalent vaccine), but with lesser type-specific efficacy. Considering constant vaccination controls, the disease-free equilibrium and the effective reproduction number $\mathcal{R}_v$ for the autonomous model are computed in terms of the model parameters. Local-asymptotic stability of the disease-free equilibrium is established in terms of $\mathcal{R}_v$. Uncertainty and Sensitivity analyses are carried out to study the influence of various important model parameters on the HPV infection prevalence. Assuming the HPV infection prevalence in the population under the constant control, optimal control theory is used to devise optimal vaccination strategies for the associated non-autonomous model when the vaccination rates are functions of time. The impact of these strategies on the number of infected individuals and the accumulated cost is assessed and compared with the constant control case. Switch times from one vaccine combination to a different combination including the nonavalent vaccine are assessed during an optimally designed HPV immunization program.



## 1. Introduction

With over 100 known phenotypes of human papillomavirus (HPV), about 40 are the leading cause of genital infections in both males and females (Malik et al., 2013a). Thirteen or so (oncogenic) types can potentially lead to cancers predominantly including cervical cancer in women. Most HPV infections are asymptomatic and clear spontaneously. Persistent infections may progress to advanced stages and take many years to lead to cancer. We refer the readers to Bosch et al. (1995, 2002) for studies on the association between HPV infection and cervical cancer. Trottier et al. (2006) study the association between multiple HPV types and cervical cancer to conclude that infections with multiple HPV types act synergistically in cervical carcinogenesis. Immunization is the most effective infection transmission control strategy and clinical trials have demonstrated that vaccination offers the greatest protection against HPV infections.

HPV vaccination is widely endorsed by health regulators of several countries and publicly funded in the United States of America, Canada, Australia, many European countries, some Latin American countries, and the United Arab Emirates (Bornstein, 2010). Clinical recommendation advocates vaccine administration for both sexes (males and females) targeting the age group of 9–26 years. The HPV vaccines currently endorsed for use in the USA, Canada, many European countries and the UAE are Merck's quadrivalent vaccine Gardasil (which targets HPV 6, 11, 16 and 18) and GlaxoSmithKline's bivalent vaccine Cervarix (which targets HPV 16 and 18). The reasons for this concurrent use in the vaccination programs include the fact that the two vaccines have different anti-dysplastic/anti-neoplastic properties and have some non-overlapping intended benefits: the bivalent vaccine is expectedly more effective against cervical intraepithelial neoplasia (CIN2 and 3) and squamous cell carcinoma (SCC) in the long term, and the quadrivalent vaccine is better at reducing anogenital warts (Van de Velde et al., 2012) and at preventing CIN 1, and vulvar and vaginal intraepithelial neoplasia (Bornstein, 2010). The bivalent vaccine is also potentially capable of conferring a longer duration of protection (Van de Velde et al., 2012; Bornstein, 2010). A third, nonavalent vaccine (Gardasil 9), has been approved by the US Food and Drug Administration in December 2014 and by Health Canada in February 2015. Gardasil 9 will target HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58, the types which are known to cause 90% of cervical

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cancers globally. The inclusion of the nonavalent vaccine in public vaccination programs has the potential to further reduce precancerous lesions and cervical cancer.

Several mathematical models have been developed to model disease-spread, infection control and development of suitable control strategies. Related to HPV, Elbasha and Galvani (2005) develop a mathematical model to explore how the interaction among HPV types amplifies or attenuates the effectiveness of vaccination programs in reducing the prevalence of the HPV types associated with cervical cancer, and conclude that under synergistic interaction among different HPV types a mass vaccination may reduce the prevalence of types including those not actively targeted by the vaccine. Dasbach et al. (2006) survey different types of HPV mathematical models reported in the literature including cohort, population dynamic, and hybrid type to provide insight to the policy makers by projecting the long-term epidemiologic and economic consequences of vaccination, and evaluate alternative policies.

Ault (2007) discusses the impacts of long-term vaccine efficacy with regard to invasive cervical cancer. Van de Velde et al. (2007) use a cohort model measuring parameter uncertainty to predict the impact of HPV 6, 11, 16, 18 vaccination concluding that vaccinating girls aged 12 years with vaccine efficacy of 95% (and assuming no diminishing of effects) would reduce their lifetime risk of HPV infection, CIN1, CIN2/3, and SCC. Elbasha et al. (2007) present a transmission dynamic model to assess the epidemiologic consequences in administering a prophylactic quadrivalent vaccine, and conclude that vaccinating girls before the age of 12 years is cost effective and would reduce the incidence of genital warts by 83% and cervical cancer by 78% in an organized setting of cervical cancer screening in the United States. Additionally, only the quadrivalent vaccine is recommended for boys and men and Elbasha et al. (2007) also show that including males in the immunization program is the most effective strategy leading to reduction in the incidence of genital warts, cervical intraepithelial neoplasia, and cervical cancer by 97%, 91%, and 91%, respectively.

Elbasha (2008) develops a two-sex, deterministic compartmental model based on susceptible-infective-removed (SIR) structure to derive basic and effective reproduction numbers and a measure of vaccine impact. Elbasha and Dasbach (2010) use a mathematical population model to assess the public health impacts incorporating direct and indirect protective effects of HPV vaccination in boys and men with the quadrivalent HPV vaccine in the United States. Brisson et al. (2011) use a stochastic individual-based transmission dynamic model to illustrate and compare the population-level impact of each HPV vaccine type. Van de Velde et al. (2012) compare potential population-level effectiveness of the bivalent, quadrivalent, and candidate nonavalent HPV vaccines. They conclude that the bivalent vaccine is expected to be slightly more effective at preventing CIN2, CIN3 and SCC in the longer term, whereas the quadrivalent vaccine is expected to substantially reduce anogenital warts (AGW) cases shortly after the start of vaccination programs. Malik et al. (2013a) develop a deterministic model using non-linear partial differential equations with separable transmission coefficients, showing that the disease-free equilibrium of the model is locally asymptotically stable whenever the effective reproduction number ($\mathcal{R}_v$) is less than unity. It is shown to be globally asymptotically stable in the presence of additional conditions. The model has at least one endemic equilibrium when $\mathcal{R}_v$ exceeds unity. Malik et al. (2013b) use an ordinary differential equations based mathematical model for HPV to assess the impact of a hypothetical anti-HPV vaccine and Pap cytology screening, to reaffirm the recommendations of health regulatory agencies in the USA to offer Pap screening on a 3-year basis replacing the need for annual screenings.

A mathematical model is constructed and analyzed in this paper to find the optimal vaccination rates of the bivalent, quadrivalent and nonavalent vaccines at a given time during a vaccination program if all three vaccines are in use simultaneously against the nine aforementioned HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58, henceforth referred to as vaccine-targeted types), and to investigate an optimal vaccination strategy if the bivalent and quadrivalent vaccines are initially under use and during the program one or both are replaced by the new, nonavalent vaccine. The model assumes that only susceptible female population is vaccinated, and an individual can be vaccinated with one of the three vaccines. The bivalent vaccine has a positive efficacy against HPV types 16 and 18. Phylogenetically HPV 16 is closely related to HPV 31, and HPV 18 to HPV 45, and Cervarix has been observed to be efficacious against HPV 31, 33, 45 and 52 (Bornstein, 2010). It is therefore assumed in the model that the bivalent vaccine offers cross-protection against these types, but is ineffective against other vaccine-targeted types; the quadrivalent vaccine has a positive efficacy against HPV types 6, 11, 16 and 18 but is ineffective against all other vaccine-targeted types; the nonavalent vaccine has a positive efficacy against all vaccine-targeted HPV types but the efficacy of the quadrivalent and the nonavalent vaccines wanes quicker than that of the bivalent vaccine (Van de Velde et al., 2012; Bornstein, 2010; Verheijen, 2011).

The efficacy comparison of the bivalent and quadrivalent vaccines is debated in the literature (for example see Bornstein, 2010; Verheijen, 2011). Whereas the quadrivalent Gardasil has shown better effectiveness against low-grade CIN caused by HPV 6 and 11 and vulvar and vaginal precancer/lesions than Cervarix, the later is more efficacious against cancerous types HPV 31, 45 and 52 than Gardasil (with similar potential against HPV 31) (Bornstein, 2010). Bornstein (2010) notes that such comparisons of the Phase III studies are limited because of the differences in the goals, the investigated variables and the inclusion criteria. Multiple comparative studies are needed for conclusive claims. Furthermore due to protection against a broader range of HPV types, the nonavalent vaccine is assumed to have a lower type-specific efficacy than the quadrivalent vaccine.

Certain public health programs may have no choice (due to the affordability and other related factors) to recommend only one or two of the three HPV vaccines. The health authorities then have various characteristics of the vaccines to compare to be able to decide which vaccine is more efficacious, using a measure that suits the circumstances of the health program. The parameters of this measure may include cost effectiveness, higher and more sustained immune response, duration of protection, efficacy against multiple HPV types, protection against multiple cancers, and prevention of death from cervical cancer versus morbidity from warts (hence evaluating in terms of quality adjusted life years) (Verheijen, 2011).

The remainder of the paper is organized as follows. The next section describes the model formulation. In Section 3 a threshold quantity namely the effective reproduction number ($\mathcal{R}_v$) is computed assuming constant vaccination rates corresponding to each type of vaccine. This approach examines the role of HPV transmission parameters in reducing the prevalence of the disease. Time dependent control strategies are then studied in the form of time dependent vaccination rates to determine HPV control programs through setting a goal to minimize the number of individuals infected with HPV and simultaneously minimizing the cost of vaccinating with each type of vaccine. Section 4 describes the optimal control strategy with the three vaccine types, the consequent total infected population and the associated accumulated cost. Optimal control theory is used to design an optimal vaccination program that utilizes the (i) cross-protection and long-lasting effectiveness associated with the bivalent vaccine, (ii)