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A model to assess the effect of vaccine compliance on Human Papillomavirus infection and cervical cancer

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ABSTRACT

Three doses of a Human Papillomavirus (HPV) vaccine are recommended for both males and females, and compliance is a major challenge. In this paper a deterministic model for HPV infection and cervical cancer is constructed and rigorously analyzed for the effects of vaccine compliance. The model is based on ordinary differential equations and incorporates cohort vaccination of males and females before entering the sexually-active class as well as a fraction that starts taking the vaccine after entering the sexually-active class. The female population is further stratified into two age groups. The first group is at a higher risk for new HPV infection, is not likely to develop cervical cancer, and is subject to three doses of an HPV vaccine. The second age group has reduced chances of acquiring new infections but is at a higher risk for developing cervical cancer resulting from a persistent HPV infection. No fresh HPV vaccine is administered in this age group. The model has a locally asymptotically-stable disease-free equilibrium but may also admit endemic equilibria when the epidemic threshold, namely the effective reproduction number, $\mathcal{R}_v$, is below unity. Using the center manifold theory it is shown that the model exhibits a backward bifurcation at $\mathcal{R}_v = 1$, which is caused due to the imperfect HPV vaccine. For the case of a perfect vaccine, the disease-free equilibrium is proved to be globally asymptotically-stable, under certain additional conditions, when $\mathcal{R}_v \leq 1$. Multiple endemic equilibria may exist when $\mathcal{R}_v > 1$. It is shown through numerical simulations that vaccine compliance (with all three doses) is necessary for the reduction of HPV infections and cervical cancer. Lack of compliance may lead to a higher number of infections and cancer cases in the long run.

1. Introduction

Human Papillomavirus (HPV) is the most common viral infection of the reproductive tract. In addition to the ano-genital warts in males and females, HPV may cause recurrent respiratory papillomatosis. HPV infection is mostly asymptomatic and transient, lasting less than a year [1]. It is transmitted sexually and all sexually active individuals are at risk for HPV, with the highest infection rates being in the ages 15–24 [2] (highest prevalence in ages 16–25 [3]).

HPV vaccination in Canada using Gardasil (by Merck) is approved for ages 9–45 in females and 9–26 in males and using Cervarix (by GSK) is approved for females in ages 9–25; girls between the ages of 9 and 13 have been shown to possess the

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best levels of HPV vaccine protection [2]. In USA, Centers for Disease Control and Prevention (CDC) recommends three doses of HPV vaccine for all kids (boys and girls) of age 11 or 12, or through age 26 (females) and 21 (males) if they did not get the vaccine. In December 2014, the US Food and Drug Administration approved the recombinant Gardasil 9 for females of ages 9–26 and males of ages 9–15 [4] Gardasil 9 was also approved by Health Canada in February 2015 for females of age 9–45 and males of age 9–26. In the United Kingdom, an HPV vaccine is recommended for 12–13 year old girls (up to 18 for a catch-up vaccine) [3]. In some countries all three HPV vaccines (Cervarix, Gardasil 4 and Gardasil 9) are simultaneously under use [5].

An HPV prophylactic vaccine, in addition to protecting the immunized individuals, also indirectly protects others through herd immunity [6]. The three HPV vaccine doses may ideally be completed within a six months duration. However owing to lack of interest, motivation and education a significant proportion of the target population does not take, or complete the course of, the vaccine. See Markowitz et al. [7] for a comparison of the level of coverage achieved with all three doses among the target age groups in females, in different countries. A coverage of 39.7% in the USA among girls aged 13–17 years in 2014 [8], exhibits a nominal increase from 32% in 2010 [7]. Of those who start taking the vaccine, commitment for the completion of all three doses fades with time. For example, CDC's Morbidity and Mortality Weekly Report [9] found that in 2011, among the US males 13–17 of age, 8.3% had received one or more doses and only 1.3% had taken all three. Among females of the same age group, 53% had taken one or more HPV vaccine doses but 34.8% received $\geq$ 3 doses. The report concludes that 'at only 30.0% in 2011, coverage among females aged 13–15 years is far short of the *Healthy People 2020* target of 80% coverage for $\geq$ 3 HPV vaccine doses.'

Persistent HPV infection is the leading cause of cervical cancer, the second most frequent cancer (after breast cancer) in women aged 20–44 [2] (20–49 according to Brisson et al. [10]). Pap test is recommended for women aged 21–65 (CDC, [2]). Other cancers (e.g. penile) are relatively less frequent and less conclusively linked to HPV as a cause.

Indeed it may take decades after acquiring HPV infection to develop pre-invasive cervical lesions and cancer [11]; the slow and complex cervical carcinogenesis is described in Malik et al. [1] and references therein. Sasieni and Castanon [12] note that the incidence of cervical cancer in women under 25 years in England is low (peak CIN3 incidence rates are observed in women aged 25–29, though not all CIN lesions develop into cancer). The same authors observe that the cancer rates are, in absolute terms, appreciable at 25 years of age for most countries studied, and 30 years in Finland, Netherlands and Japan in particular.

Cervical cancer is uncommon in females under the age of 30 and is practically non-existent before 20 years of age [13] (about 95% cases occur in women aged 30 and above, while only 1% occur before 25). Data for Quebec for the years 2001–2005 presented in Goggin and Mayrand [13] confirms that the incidence rate of cervical cancer is minimal before the age of 30 and spikes between the ages 35 and 50 (with a second spike among women 75 and above). The US data reported in references of (and the trajectory followed closely by the model presented in) Elbasha et al. [6] suggest that in the absence of an HPV vaccine, the steady-state HPV 6/11/16/18-related cervical intraepithelial neoplasia (CIN) grade 2 incidence is less than 30 per 100,000 in the ages below 15 and slightly over 30 in ages 15–19, which nearly quadruples (about 130 per 100,000) in the age group 20–29. Likewise the HPV 16/18-related CIN 3 incidence is less than 25 per 100,000 in ages below 19, over 90 in age the group 20–39 (peaks at a little less than 300 per 100,000 in the age group 25–29).

It is clear that age is an important player in the HPV transmission and acquisition, a factor of high consideration in the HPV vaccination programs, and a significant determinant of the incidence of the cervical cancer. It is therefore instructive to stratify the female population into two age groups, one being more significant for HPV infection and the other more significant for cervical cancer. The borderline age is certainly debatable, vague, country-dependent, and subject to unusual circumstances. Multiple mathematical models of HPV infection have been published that stratify the population by age (see, for example, [14–17]).

In the model constructed in this work, females in the first age group are considered more susceptible to HPV infection and subject to recommended vaccines (including the catch-up vaccine). No possibility of cervical cancer is assumed in this age group. The second age group is assumed to be at a reduced risk of new HPV infection but is more prone to exhibit persistent infection leading to cervical cancer. This age group does not acquire fresh HPV vaccine. The borderline age, for the purpose of approximating certain model parameters, for the numerical simulations, is assumed to be 26 years.

2. Model formulation

The model is formulated as follows. The total sexually active female population at time t, denoted by $N_f(t)$, is divided into two major age-groups, the first (denoted with subscript 1) more significant for HPV infection and subject to three doses of an HPV vaccine and the second (denoted with subscript 2) more significant for persistent infection which may lead to cervical dysplasia and cancer. The first group comprises, at time t, the unvaccinated susceptible ($S_1(t)$), susceptible females vaccinated with the first, second, and third doses respectively ($U_1(t), V_1(t), W_1(t)$), those exposed to HPV infection ($E_1(t)$), HPV-infected ($I_1(t)$) and recovered from the infection ($R_1(t)$). The second group is divided into sub-populations of unvaccinated susceptible ($S_2(t)$), susceptible females vaccinated with the first, second, and third doses respectively ($U_2(t), V_2(t), W_2(t)$), those exposed to HPV infection ($E_2(t)$), HPV-infected ($I_2(t)$), recovered from the infection ($R_2(t)$), HPV-infected with persistent infection ($P(t)$), individuals with CIN ($Q(t)$), those with cancer ($C(t)$), and those who recovered from cancer ($R_c(t)$). Hence,