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Cost-effectiveness of sex-neutral HPV-vaccination in Sweden, accounting for herd-immunity and sexual behaviour

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ABSTRACT

Introduction: The aim was to assess cost-effectiveness of expanding the Swedish HPV-vaccination program to include preadolescent boys, by comparing health-effects and costs of HPV-related disease, with a sex-neutral vaccination program versus only vaccinating girls.
Methods: We used a dynamic compartmental model to simulate the burden of HPV16/18-related disease in Sweden, accounting for indirect effects of vaccination through herd-immunity. The model accounted for sexual behaviour, such as age preferences and men who have sex with men. The main outcome was number of individuals with HPV-related cancers (cervical, genital, anal and oropharyngeal cancer) and cervical intraepithelial neoplasia (CIN). Costs included in the analysis were those incurred when treating HPV-related cancer and CIN, production losses during sick-leave, and acquisition and administration of vaccine. Health effects were measured as quality-adjusted life years (QALY). The time horizon was set to 100 years, and both effects and costs were discounted by 3% annually. Health effects and costs were accumulated over the time horizon and used to create an incremental cost-effectiveness ratio.
Results: A sex-neutral vaccination program would reduce HPV-related cancer and CIN, both due to direct effects among vaccinated as well as through herd-immunity, further decreasing HPV-related cancer burden annually by around 60 cases among men and women respectively in steady-state. The cost per gained QALY was estimated to 40,000 euro. Applying the procurement price of 2017, sex-neutral vaccination was dominant.
Conclusion: Introducing a sex-neutral HPV-vaccination program would be good value for money also in Sweden where there this 80% coverage in the current HPV-vaccination program for preadolescent girls. The cost-effectiveness of a sex-neutral program is highly dependent on the price of the vaccine, the lower the price the more favourable it is to also vaccinate boys.

1. Introduction

Since vaccination against human papilloma virus (HPV) in Swedish schools started for girls in 2012, the mean national coverage has been around 80% for one dose [1]. It has been argued that increasing the uptake among girls could have a greater impact on the burden of HPV-related disease than also introducing vaccination for boys [2,3]. However, increasing the coverage among girls in settings where the coverage is already high may be more difficult to achieve than to vaccinate a moderate proportion of boys.

HPV is considered to be the most prevalent sexually transmitted infection in both men and women. Over 200 types of HPV have been identified, of which 40 types are known to be sexually transmitted [4]. Around 90% of HPV infections are transient and cleared within 1–2 years, but some infections persist and may cause a range of clinical states, including anogenital warts, precancerous lesions, and cancer [5]. The thirteen HPV-types known to cause cervical cancer, also contribute to cancer in the anogenital region, such as cancer of the vagina, vulva, anus, and penis as well as in the oropharynx, mainly tonsillar and base of tongue cancer [6,7]. HPV

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16 is the dominating cause of non-cervical HPV-related cancer [6,8]. All three of the available vaccines specifically target HPV 16 and 18.

Oropharyngeal cancer mainly occur among men, and have increased rapidly in incidence in western countries over the last few years [9–13], and is today the second most common head and neck cancer in Sweden with 384 new cases diagnosed in 2015, 71% among men [14,15]. Around 100 men are diagnosed with invasive penile cancer annually [16]. Around 150 individuals are diagnosed with anal cancer annually in Sweden, 30% among men [17].

The introduction of HPV vaccination for girls in Sweden has led to a reduction in HPV infections [18], cervical intraepithelial neoplasia (CIN) [19] and genital warts [20] among women. Clear herd immunity effects among both women and men have been demonstrated in other countries with vaccination programmes for girls, [21] and recently also shown for sex-neutral vaccination programmes [22,23]. The follow-up time within national HPV vaccination programmes is still too short to evaluate the effect on cancer, although this has recently been demonstrated in one of the major HPV vaccine trials [24]. Only a few countries have implemented sex-neutral vaccination programmes against HPV. Some countries have instead implemented risk-group vaccination programmes offering HPV vaccination to men who have sex with men (MSM). The effect of introducing HPV vaccination for boys thus has to be modelled in order to estimate the effect on HPV-related cancer, using current cancer incidence data and estimates of the contribution of vaccine-preventable HPV-infection.

We modelled the effect of girls-only versus sex-neutral HPV vaccination programmes on health outcomes in both sexes, mainly HPV-related cancer and CIN incidence. Adding further to previously conducted modelling work, our model accounts for herd immunity and MSM. A cost-effectiveness evaluation was performed to evaluate sex-neutral HPV vaccination.

2. Method

2.1. Model overview

HPV-related cancer was modelled using a Markov multi-state model that accounted for herd immunity. The model was formulated as a system of differential equations that described the rate of change in the number of people in each health state in the population over time. The rate at which individuals were diagnosed with cancer or CIN and at what severity-state, was determined by the average incidence in Sweden between 2010 and 2014 (Table 2). The model was calibrated to fit historical data on HPV-related cancers and CIN [25,26].

The inflow in the model was based on a 2015 birth cohort and the outflow was either through cancer-related death or natural mortality. The individuals entered the model in the health state of "susceptible", and depending on the vaccination coverage, a proportion moved on to the health state "vaccinated". Those who were vaccinated received protection corresponding to the effectiveness of the vaccine. The health state of "HPV-related disease" in Fig. 1 represents CIN and the HPV-related cancer types: cervical, vaginal, vulvar, anal, and oropharyngeal (tonsillar and base of tongue) cancer for women and penile, anal and oropharyngeal cancer for men. Each of the diseases was modelled separately, with separate effects of vaccination and burden of disease. If an individual developed cancer he or she was assumed to stay in that health state for 5 years, before moving on to "recovered".

Boys and girls were modelled separately and affected each other through herd immunity that was accounted for using a previously developed method [27], where an adjustment term related to the proportion of vaccinated of the opposite sex was applied to the risk of HPV-related disease. In terms of age mixing, it was assumed that 90% of the individuals in the population had sexual contacts within 10 years of their own age. MSM were assumed not to be protected through herd immunity when only girls were vaccinated. MSM were estimated to be 2.5% of the male population [28]. The two sub-models (boys/girls) were in turn divided into eight sub-sub-models, each one corresponding to one age-group (10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–84, 85+ years). Movements between sub-sub-models occurred annually and was determined by the age structure of the age-group.

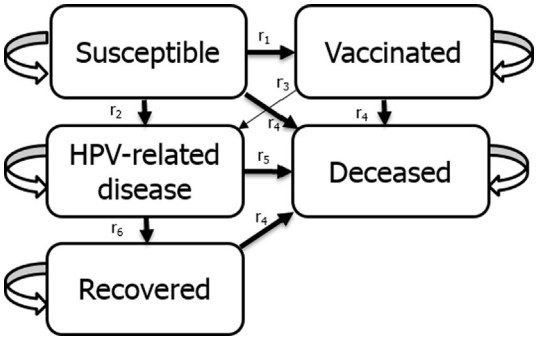

Fig. 1. Stylized compartmental model for HPV-related disease. r_1 = vaccination coverage. R2 = incidence rates for HPV-related cancer and CIN, by sex and age. R3 = incidence rated among vaccinated ("non-responders") for HPV-related cancer and CIN, by sex and age. R4 = rates of all-cause mortality from population lifetables by sex and age. R5 = excess mortality rates of death due to HPV-related cancer, by sex and age. R6 = rates of recovered from HPV-related cancer and CIN, by sex and age.

The national HPV vaccination programme aims to decrease HPV-related cancer in the population, and the model therefore focused on cancer and CIN. The key outputs of the model include: (1) number of incident cases of cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancer averted, (2) number of CIN averted and, as a sensitivity analysis, and (3) number of cases with anogenital warts averted.

2.2. Model input parameters

To calculate the risk of HPV-related cancer and CIN, first the average incidence of cervical, vaginal, vulvar, penile, anal and oropharyngeal cancer and CIN, by age-group and sex, for the years 2010–2014 were extracted and then the proportion of cases that could be attributed to HPV, and thus be affected by vaccination, were calculated (Table 2).

The different diseases were divided into two or three severity-states. The definition of these severity-states, denoted as A, B and C, is presented in Table 1. The 5-year relative survival was dependent on cancer type, age at diagnosis, and severity-state.

A vaccination coverage of 80% was assumed among boys, corresponding to the coverage achieved among girls in the current vaccination programme in Sweden for one dose [1]. As stated by the Global Advisory Committee on Vaccine Safety (GACVS) [29] the HPV vaccine is very safe, and adverse events are mainly mild local site reactions. Adverse events were therefore not considered in the model. The vaccine effectiveness in the model was HPV-type specific, and vaccination was assumed to provide life-long protection. The vaccine was assumed to be 100% effective against HPV-types 16/18, and the vaccine effectiveness against each HPV-related cancer or CIN was therefore dependent on the estimated proportion caused by HPV 16/18.

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