Vaccine 30 (2012) 425–435

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Time for change? An economic evaluation of integrated cervical screening and HPV immunization programs in Canada

Stephen P. Tully[a], Andrea M. Anonychuk[b,c], Diana Maria Sanchez[d], Alison P. Galvani[d], Chris T. Bauch[a,e,*]

[a] Department of Mathematics and Statistics, University of Guelph, Canada
[b] Leslie Dan Faculty of Pharmacy, University of Toronto, Canada
[c] GlaxoSmithKline Biologicals, Wavre, Belgium
[d] School of Public Health, Yale University, USA
[e] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Canada

ARTICLE INFO

Article history:
Received 4 March 2011
Received in revised form 24 October 2011
Accepted 26 October 2011
Available online 7 November 2011

Keywords:
Human papillomavirus vaccine
Catch-up immunization
Dynamic model
Cervical screening
Cervical cancer
Cost-utility analysis

ABSTRACT

Many jurisdictions have implemented universal human papillomavirus (HPV) immunization programs in preadolescent females. However, the cost-effectiveness of modified cervical screening guidelines and/or catch-up immunization in older females in Canada has not been evaluated. We conducted a cost-utility analysis of screening and immunization with the bivalent vaccine for the Canadian setting from the Ministry of Health perspective. We used a dynamic model to capture herd immunity and included cross-protection against strains not included in the vaccine. We found that adding catch-up immunization to the current program would be cost-effective, and that combining catch-up immunization with delaying the age at which screening is first initiated could result in cost savings and net health gains.

1. Introduction

Cervical cancer continues to impose a considerable burden worldwide despite reduced incidence after the implementation of cervical cancer screening in the 1960s [1,2]. In 2009 alone, an estimated 1300 women were diagnosed with cervical cancer and approximately 390 women died of this disease in Canada [3]. The estimated cervical cancer incidence in Canadian provinces ranges from 7 to 10 per 100,000 females per year, with the highest incidence occurring women aged 40–69 [4,5].

The guidelines for cervical cancer screening in Canada state that all women aged 18 and over should be screened, initially with two smears one year apart. If these smears are within normal limits, then rescreening every three years is advised until the age of 69 [6]. The success of this program is reflected in the participation rate of women. The best national data currently available show 1-year participation rates do not vary greatly among provinces, ranging from 37% in British Columbia and Ontario to 44% in Nova Scotia with a 3-year participation rate of approximately 70% [7] across the country.

In the 1980s, infection by certain human papillomavirus (HPV) types was identified as a prerequisite for development of cervical cancer [8,9]. High-risk HPV types 16 and 18 have been identified as being present in approximately 70% of cervical cancers [9]. Recently, two vaccines were developed that are effective in preventing HPV infection and development of pre-cancerous cervical lesions associated with types 16 and 18 [10,11]. HPV vaccines are changing the landscape of cervical cancer prevention and treatment, with promise to reduce cervical cancer incidence still further.

Mathematical models can be used to project future costs and health outcomes of HPV immunization under various alternative immunization or screening strategies [4,12–38]. These modeling studies have investigated topics such as [1] the cost-effectiveness of universal HPV immunization in pre-adolescent females compared to no immunization; [2] the effectiveness of different immunization strategies in reducing prevalence of lesions and cervical cancer over time; [3] the cost-effectiveness of vaccinating males; and [4] determining the number of women who need to be vaccinated to prevent one cervical cancer case or death.

However, the implementation of universal immunization programs for pre-adolescent females in many jurisdictions has generated new questions regarding screening and immunization

* Corresponding author at: Department of Mathematics and Statistics, University of Guelph, 50 Stone Road East, Guelph, ON N1G 2W1, Canada. Tel.: +1 519 824 4120; fax: +1 519 837 0221.
E-mail address: cbauch@uoguelph.ca (C.T. Bauch).

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doi:10.1016/j.vaccine.2011.10.067

strategies. For example, how effective and cost-effective, are catch-up immunization programs in older females who have not been vaccinated? Should screening recommendations change in response to the implementation of HPV immunization programs? What combined immunization/screening strategies are most effective for preventing cervical cancer and provide the best value for money? Moreover, emerging data from clinical trials may impact model predictions. For example, both bivalent and quadrivalent vaccines now report significant cross-protection against infection and high-grade lesions caused by high-risk HPV types not included in the vaccine, although differences between the two vaccines with respect to cross-protection and other parameters are also becoming more clear [10,39–42].

Our objective was to conduct an economic evaluation of [1] catch-up immunization programs in older females [2], starting cervical screening at a later age than in current practice, and [3] possible combinations of these two strategies, in a population where a universal HPV immunization program of pre-adolescent females is already in place. We conducted a cost-utility analysis based upon a dynamic (transmission) model. Cost utility analyses estimate the costs required per quality-adjusted-life-year gained by implementing an alternative strategy, relative to the current strategy. Transmission models are useful for capturing transmission mechanisms and hence herd immunity effects, which can alter cost-effectiveness estimates considerably [43,44].

We parameterized the model with recently published data on properties of the bivalent vaccine, which is now licensed for use in Canada. Despite differences between the bivalent and quadrivalent vaccines in terms of strain composition, immunogenicity, cross-protection properties, and (possibly) efficacy in older women with previous exposure to HPV [10,40–42], the bivalent vaccine has been evaluated less frequently than the quadrivalent vaccine, hence our economic evaluation will focus on the bivalent vaccine. Our model is tailored as closely as possible to Canada, where many provinces have implemented universal school-based programs and where a single payer (the Ministry of Health) is often responsible for supporting both immunization programs and cervical screening programs.

2. Methods

2.1. Model structure

An age-structured compartmental model of HPV transmission and immunization with the bivalent vaccine was developed. The population was stratified by age (15–19, 20–24, 25–34, 35–44, 45–54, 55–64, 65+), gender (male, female), disease status (for females: susceptible, infected, natural immunity, vaccine immunity, cervical intraepithelial (CIN) grade 1 lesion, CIN2/3 lesion, or squamous cell carcinoma (SCC); for males: susceptible, infected, or natural immunity); and HPV type (16/18, or other high-risk). All transitions for demographic processes, natural disease history, infection and immunization are illustrated in Fig. 1 for type 16/18 infection in a typical age class of females and males. The parameter definitions and parameter values corresponding to each transition are in Tables 1 and 2, and costing parameters are in Table 3, together with the data sources [1,4,10,20,21,45–77]. Full model equations are included in the Supplementary File (Sections S1 and S2).

2.2. Demographic processes

Males and females were recruited (i.e., entered the model population) at age 15. (The average age of onset of sexual intercourse is approximately 14–15 in the general Canadian population [78]; vaccination at age 12 was accounted for by adjusting the compartmental sizes upon recruitment as required.) The size of each birth cohort equaled the average size of a typical Ontario birth cohort. Age-specific death rates due to other causes were applied to males and females. Age-specific benign hysterectomies were also included for females.

2.3. Natural disease history assumptions

Progression from infected to CIN1, infected to CIN2/3, and CIN1 to CIN2/3 occurred at specified rates. Regression also occurred from CIN1 to infected, CIN2/3 to CIN1 and CIN2/3 to infected at specified rates. Individuals cleared the infected state at a specified rate, acquiring natural immunity. Natural immunity to HPV is weak [48,49], hence we assumed that individuals lost natural immunity at a specified rate, becoming fully susceptible again. Individuals progressed from CIN2/3 to squamous cell carcinoma (SCC) at a specified rate, and did not regress from SCC. A separate submodel tracked progression from SCC stages I to IV (see Supplementary File, Section S3). The output of this submodel was used to assign a cost and QALY penalty per incident case of SCC, which was combined with the incidence of SCC predicted by the dynamic model to predict the total impact of SCC on costs and QALYs over time. Replacement effects caused by "unmasking"—progression of other-high-risk lesions that would have been removed through treatment in the pre-vaccine era—were also included and depended on the assumed vaccine coverage rate [46,61] (Supplementary File, Section S4). It was assumed that progression of type 16/18 infections and progression of other high-risk types were otherwise independent.

2.4. Transmission assumptions

It was assumed that sexual mixing was age-assortative, with males and females tending to pick sexual partners close in age, but the male typically being a few years older than the female [47]. For type 16/18 infection, the probability of a susceptible female of age group *i* being infected by an infected male of age group *j* depended on the proportion of contacts of females in age group *i* that occurred with males in age group *j* according to the age-assortative mixing considerations; the percentage of males in age group *j* currently infected; and a fitted parameter representing the transmission rate. The transmission rate parameter was further adjusted for age-related and gender-related differences (male to female versus female to male) in transmission probability. Age-related variation was allowed because epidemiologically relevant factors such as frequency of sexual intercourse, partnership turnover rate, and sexual network structure also vary with age [47,79,80]. The free parameters were fitted according to a filtering methodology described in Section 2.7. Transmission was modeled the same way for infection by other high-risk types, and for the rate at which females infected males. The mathematical equations representing the transmission processes appear in the Supplementary File, Sections S1 and S2.

2.5. Intervention assumptions

We assumed use of the bivalent vaccine, which has a high efficacy (>90%) against incident and persistent type 16/18 infections [81]. Moreover, data from a double-blind, randomized study indicate that it also provides partial efficacy (∼12%) against infection by other high-risk types not included in the vaccine [10]. The same study furthermore indicates that the efficacy of the vaccine in preventing CIN2+ lesions by twelve common non-16/18 high-risk types is 37% after adjusting for co-infections (54% before adjusting for co-infections) [10].

We modeled vaccine protection against primary infection by types 16 and 18 by moving a proportion ε of vaccinated individuals