VALUE IN HEALTH REGIONAL ISSUES 2 (2013) 92–97

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The Cost-Effectiveness Analysis of a Quadrivalent Human Papillomavirus Vaccine (6/11/16/18) for Females in Japan

Kaoru Yamabe, MSc[1,], Puneet K. Singhal, PhD[2], Machiko Abe, MSc[1], Erik J. Dasbach, PhD[3], Elamin H. Elbasha, PhD[3]*

[1]*MSD.K.K., Tokyo, Japan*; [2]*Merck & Co., Inc., West Point, PA, USA*; [3]*Merck & Co., Inc., North Wales, PA, USA*

ABSTRACT

Objective: We assessed the epidemiological and economic impact of a quadrivalent human papillomavirus (HPV) (6/11/16/18) vaccine for females in preventing cervical cancer, cervical intraepithelial neoplasia grades 2 and 3 (CIN 2/3), cervical intraepithelial neoplasia grade 1 (CIN 1), and genital warts in Japan by using a transmission dynamic model. **Methods:** A published mathematical model of the transmission dynamics of HPV infection and disease was adapted for Japan. Model inputs were used from Japan or the Asia/Pacific region when available; otherwise, the default values in the original model were used. The transmission dynamic model was used to assess the epidemiological and economic impact of a quadrivalent HPV (6/11/16/18) vaccine for females in preventing cervical cancer, CIN 2/3, CIN 1, and genital warts in Japan.Maintaining current cervical cancer screening practices, we evaluated two strategies: routine vaccination of females by age 12 years (S1), and S1 combined with a temporary (5 years) female catch-up program for age 12 to 24 years (S2). The vaccine coverage rate was 80% for the routine and 50% for the catch-up vaccination programs. **Results:** Compared with no vaccination, both vaccination strategies significantly reduced the incidence of HPV 6/11/16/18–related disease. The most effective strategy was S2. By using this strategy over 100 years in the Japanese population, the estimated cumulative percentage reduction in incident HPV 6/11/16/18–related genital warts-female, genital warts-male, cervical CIN 1, CIN 2/3, and cervical cancer cases was 90% (2,113,723 cases), 86% (2,082,637 cases), 72% (263,406 cases), 71% (1,328,366 cases), and 58% (323,145 cases), respectively. The cost-effectiveness ratios were JPY 1,244,000, and JPY 1,205,800 per quality-adjusted life-year gained for S1 and S2 compared with no vaccination, respectively, over a time horizon of 100 years. **Conclusion:** We conclude that a quadrivalent HPV vaccination program for females can reduce the incidence of cervical cancer, CIN, and genital warts in Japan at a cost-per-quality-adjusted life-year ratio within the range defined as cost-effective.

Keywords: cervical intraepithelial neoplasia, cost-effectiveness analysis, epidemiology, human papillomavirus, uterine cervical neoplasm, vaccines.

Introduction

In Japan as well as in the world, the second most common cancer in women is cervical cancer after breast cancer. Each year, approximately 10,000 cases are diagnosed, 3000 of which result in death [1,2]. In 2004, the Ministry of Health, Labor and Welfare introduced the screening test for women older than 20 years to prevent cervical cancer; however, the screening rate is quite low in comparison with other developed countries [3]. Cervical intraepithelial neoplasia (CIN) marks the precancerous stages of cervical cancer, starting with the mild dysplasia (CIN 1), progressing to the more serious forms of CIN 2 and CIN 3, and finally progressing to carcinoma. Cervical cancer is known to be caused by infection with human papillomavirus (HPV) [4,5]. Although more than 100 types of the virus have been identified [6], types 16 and 18 in particular are known to be oncogenic and associated with about 70% of the cases of cervical cancer [7]. Infection with the low-risk types of HPV 6 and 11 causes about 90% of the cases of condylomata acuminatum (genital warts) [8]. In 2011, GARDASIL was approved and is now available in Japan for females with the indications for the prevention of the following diseases caused by HPV types 6, 11, 16, and 18: cervical cancer (squamous cell cancer and adenocarcinoma) and their precursor lesions (CIN 1/2/3 and cervical adenocarcinoma in situ), vulvar intraepithelial neoplasma grade 1/2/3 and vagional intraepithelial neoplasma grade 1/2/3, and genital warts (condyloma acuminate).

It is not mandatory to submit cost-effectiveness analysis results for regulatory approval, and decision makers such as government are not required to consider economic perspectives when determining the value of drugs and funding financial resources for vaccination programs in Japan. They have recently become conscious, however, whether to be cost-effective or not so as to allocate limited resources appropriately because of the severe budget constraints and the coming superaged society that will have to bear a significant increase in medical costs.

In this report, the authors review the results from a previously developed health economic model [9] adapted to explore the epidemiological and economic consequences of introducing a quadrivalent HPV vaccine for females in Japan. Specifically, we examined the potential population-level health impact of the

Conflict of Interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

* *Address correspondence to*: Kaoru Yamabe, MSD.K.K. 1-13-12 Kudan-kita, Chiyoda-ku, Tokyo 102-8667, Japan.
E-mail: kaoru.yamabe@merck.com.

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http://dx.doi.org/10.1016/j.vhri.2013.02.001

vaccine on HPV-related diseases including cervical cancer, CIN, and genital warts, and associated health care costs from the payer perspective. We also examined the cost-effectiveness of a quadrivalent HPV vaccine program for females in Japan.

Methods

We adapted the previously developed mathematical model for evaluating the impact of quadrivalent HPV vaccination in the United States to explore the potential epidemiological and economic impact of a quadrivalent HPV vaccine in Japan. The details of this model and its structure have been previously described [9]. We modified components of the model for Japan and included cervical cancer screening rates, treatment rates, and vaccination strategies, as well as epidemiological (e.g., mortality) and economic inputs. The following text describes the strategies evaluated, model parameters and outputs, the simulation method, and the sensitivity and validation analyses.

Screening and Vaccination Strategies

Assumptions were that each vaccination strategy would be combined with current cervical cancer screening rates and HPV disease treatment practices in Japan. The base-case vaccination strategy was the routine HPV vaccination of girls by age 12 years (S1), and a catch-up vaccination program was added that targeted girls and women 12 to 24 years of age in conjunction with the base-case vaccination program for a period of just 5 years after the initiation of the vaccination program (S2).

Model Parameters and Sources

We determined baseline assumptions and estimates by a comprehensive search of the literature, input from experts, and analysis of clinical trial data [9]. Table 1 shows baseline epidemiological parameters, and Table 2 shows economic parameters and sources that we adopted.

Screening and Vaccination Program Strategy Parameters

We assumed that the period of protection for the HPV is lifetime in the base case. It was also assumed that vaccination would not have any effect on the natural course of any HPV infection that may have been present at the time of vaccination. The HPV vaccine was assumed to have an efficacy of 90% against cervical cancer caused by HPV 6/11/16/18, 95.2% against all CIN caused by HPV 6/11/16/18, and 98.9% against genital warts caused by HPV 6/11 [9]. It was assumed that up to 80% of 12-year-old Japanese girls would receive three doses and also the catch-up program for 12- to 24-year-old Japanese girls and women would receive 50% coverage by year 5.

Economic Parameters

With regard to the economic perspective in this analysis, only direct medical costs were considered. Therefore, the costs associated with work and productivity losses were not included for the analysis. Direct medical costs included the costs of vaccination, cervical cancer screening, and diagnosis and treatment of detected cervical cancer, CIN, and genital warts. We estimated direct medical costs of interventions by using the Diagnosis Procedure Combination (DPC). The cost of three-dose vaccine was assumed as ¥36,000. Costs of conventional cytology screening examinations, colposcopy, and biopsy were adopted from the official code list of the DPC and the doctors' fee schedule. Treatment costs of genital warts were also calculated by the DPC and confirmed by experts who were familiar with the treatment options and utilization in Japan. The average per-patient costs of the diagnosis and treatment of precancerous states and cervical cancer were calculated by the DPC (Table 2). Quality-adjusted life-years (QALYs) were measured by using the health utility index by weighting survival time by the quality-of-life adjustment weights–associated time in all these health states over the planning horizon [9].

The planning horizon was 100 years, and it was assumed that the population size over the 100-year horizon would be 113,843,070 (Japan population age 12 years and older in 2006). The discount rate of all costs and effects was assumed 3% per year in the base-case analysis.

Table 1 – Epidemiologic parameters.

Parameter		Reference
Demographic parameters		
Total population size	127,770,000	[23]
The female population of age 1 y and up (%)	45.9	
The male population of age 12 y and up (%)	43.2	
Incidence of HPV*-related diseases		
Number of new cases of cervical cancer	8,779	[24]
Number of cervical cancer deaths	2,481	[24]
Number of new episodes of anogenital wards	48,000	[23]
Females	21,120	[25]
Males	26,880	
Screening, Clinical diagnosis, and treatment parameters		
Age for Pap* screening begins (y)	20	
Time interval between Pap test (y)	2	
Compliance with Pap screening	23.7	[3]

Female annual all-cause mortality by age

Age group (y)	Mortality rate (%)	
0–4	0.07	
5–9	0.01	
10–14	0.01	
15–19	0.02	
20–24	0.03	
25–29	0.03	
30–34	0.04	
35–39	0.06	
40–44	0.09	[22]
45–49	0.13	
50–54	0.21	
55–59	0.29	
60–64	0.42	
65–69	0.63	
70–74	1.08	
75–79	1.94	
80–84	3.68	
85–89	7.16	
90–94	13.11	
95–99	21.51	
100+	35.86	

HPV, human papillomavirus; Pap, Papanicolaou.