9 Cost-Utility Analysis
A Case Study of a Quadrivalent Human Papillomavirus Vaccine

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CONTENTS

9.1 BACKGROUND AND INTRODUCTION

The purpose of this chapter is to introduce the reader to cost-utility analysis (CUA). We will do this by providing a brief background on CUA and reviewing a case study using it.

CUA is a special case of cost-effectiveness analysis (CEA), where the numerator of the incremental cost-effectiveness ratio (ICER) is a measure of cost (similar

to other forms of CEA) and the denominator is measured typically using a metric called the *quality-adjusted life year* (QALY). A QALY accounts for both survival and quality of life (QoL) benefits associated with the use of a healthcare technology. The QoL component of the QALY is measured using a metric known as a *health utility*; hence, the term *cost-utility analysis* is used to describe this form of CEA. Background on the measurement of health utilities is discussed in Chapter 11.

Given that the QALY can be used to measure the survival and QoL benefits of a healthcare technology, the QALY can serve as a common metric from which to compare the benefits of very different healthcare technologies (e.g., migraine pharmacotherapy versus angioplasty). Thus, one of the primary advantages of conducting a CUA is that the ICER theoretically can be considered a common metric from which to compare the relative value of one health care technology (e.g., drug) with a completely different healthcare technology (e.g., vaccine).

This universal quality of a CUA is the primary reason many policy makers and reimbursement agencies prefer or require CUA when requesting a reimbursement dossier from a manufacturer. In fact, some reimbursement agencies have established ICER thresholds from which to determine whether a healthcare technology is cost effective. For example, the National Institute for Health and Clinical Excellence (NICE) has used the benchmark ICER of £30,000 per QALY gained as a threshold from which to judge whether a drug is cost effective for the National Health Service (NHS) in England.[1,2] In the United States, $50,000 per QALY gained has been frequently used in cost-effectiveness analyses as a threshold.[3,4] From a global perspective, the World Health Organization (WHO) has established a cost-effectiveness criterion indicating that a healthcare technology is cost effective if the ICER is less than three times the per capita gross domestic product (GDP) for a given country.[5]

Other decision-makers may use "league tables" of ICERs for commonly accepted healthcare technologies (e.g., renal dialysis) as a method for judging whether a healthcare technology is cost-effective or of good value. For example, the Center for the Evaluation of Value and Risk in Health at Tufts Medical Center maintains a Cost-Effectiveness Analysis Registry.[6] In particular, the Tufts-New England Medical Center Cost-Effectiveness Registry provides public electronic access to a comprehensive database of cost-effectiveness ratios in the published medical literature that can be used by decision-makers.

To summarize, CUA can serve as a general framework for conducting economic evaluations and a practical tool for decision-makers faced with making reimbursement decisions across widely different healthcare technologies. The role of CUA in drug development, reimbursement, and marketing are described in depth in Chapter 15. In the remainder of this section, we will focus on providing an example of the methodology undertaken in developing a CUA by reviewing a case study CUA of a vaccine developed to prevent four types of human papillomavirus (HPV) infection as well as associated diseases caused by HPV infection (e.g., cervical pre-cancers, cervical cancers, and genital warts). Results from this CUA as well as other economic evaluations[7] were used by policy makers in the United States in developing vaccine recommendations for a quadrivalent HPV vaccine in 2006.

9.2 CASE-STUDY: A COST-UTILITY ANALYSIS OF A QUADRIVALENT HUMAN PAPILLOMAVIRUS VACCINATION PROGRAM

9.2.1 Background

Genital infections with HPV are among the most widespread sexually transmitted infections worldwide. Infection with HPV can cause cervical intraepithelial neoplasia (CIN); cervical, vaginal, vulvar, anal, penile, and head and neck cancers; anogenital warts; and recurrent respiratory papillomatoses (RRP). In 2006, the U.S. Food and Drug Administration approved the vaccine Gardasil® for use in girls and women 9 to 26 years of age for the prevention of the following diseases caused by HPV types 6, 11, 16, and 18:

- Cervical cancer
- Genital warts (condyloma acuminata)

and the following precancerous or dysplastic lesions:

- Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grades 2 and 3
- Vulvar intraepithelial neoplasia (VIN) grades 2 and 3
- Vaginal intraepithelial neoplasia (VaIN) grades 2 and 3
- Cervical intraepithelial neoplasia (CIN) grade 1

The Centers for Disease Control and Prevention's (CDC) Advisory Committee for Immunization Practices (ACIP) also recommended in 2006 that U.S. girls and women 11 to 26 years old be vaccinated with Gardasil (with a provision that females as young as 9 may also be vaccinated) to prevent cervical cancer, precancerous and low-grade lesions, and genital warts caused by HPV types 6, 11, 16, and 18. As part of the process for formulating this vaccine policy, CEAs of an HPV vaccine were required by the ACIP. Cost-effectiveness analyses conducted by the CDC, academia, and industry were thus presented to the ACIP. A summary of the clinical and health economic evidence considered by the ACIP, including various relevant CEAs conducted up to that time, has been reported elsewhere.[8] In this case study, we will review a cost-utility model that was developed by industry to support these deliberations. The analyses reviewed here are based on a previously published model.[9,10] For this case study, however, we will not focus on the myriad of analyses reported in these previous publications. Instead, this case study will present a few selected analyses that we develop here to specifically illustrate the value of CUA in reimbursement and policy decisions. In particular, we will highlight the role of QALYs in the analysis as this is a distinguishing feature from other forms of CEA.

9.2.2 Research Questions

The primary research questions this CUA answered were as follows:

1. In a setting of organized cervical cancer screening, what is the cost effectiveness of a quadrivalent HPV vaccination strategy that targets girls and women 12 to 24 years of age relative to a strategy of no vaccination in the United States from a healthcare system perspective over a 100-year analytic horizon?
2. In a setting of organized cervical cancer screening, is a quadrivalent HPV vaccination strategy that targets girls and women 12 to 24 years of age relative to a strategy of no vaccination in the United States cost effective?

9.2.3 Disease Model

To capture the indirect effects of vaccination on the entire population, we developed a dynamic disease transmission model.[11] Figure 9.1 depicts a simplified schematic of the health states tracked in the analysis. The model follows the U.S. population of persons greater than 12 years of age over an analytic horizon of 100 years. Persons enter the model into the susceptible state and, if vaccinated, the vaccinated state. Susceptible persons can become infected by different HPV types. Persons infected with HPV types 16 or 18 can become immune or progress to CIN 1, followed by CIN 2/3 and cervical cancer. Persons infected with HPV types 6 or 11 can become immune or progress to genital warts as well as low-grade CIN. Vaccinated persons can follow a path similar to that of susceptible individuals; however, the acquisition of infection and progression to disease is slowed through vaccination. At any point in time, persons can exit the model according to age, gender, and disease-specific mortality rates. The model consists of a system of ordinary differential equations

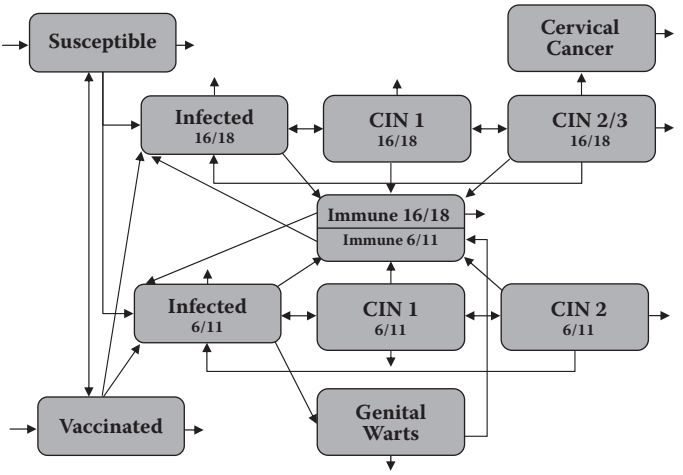

FIGURE 9.1 A simplified schematic of the HPV model.

(ODEs). We programmed all model equations and inputs in Mathematica® (Wolfram Research, Champaign, IL). We used the NDSolve subroutine in Mathematica version 5.2 to generate numerical solutions for ODEs making up the model.

9.2.4 Screening and Vaccination Strategies and Parameters

Reference Strategy. The baseline reference strategy was routine cervical cancer screening as practiced in the United States. We used age-stratified data from the Kaiser Permanente Northwest health plan, the National Health Interview Survey (NHIS), and Behavioral Risk Factor Surveillance System (BRFSS)[12,13] to estimate rates for routine cytology screening. Estimates of cytology screening test characteristics were based on published studies.[14]

Comparator Strategy. The comparator strategy (i.e., quadrivalent HPV vaccination) was assumed to be routine quadrivalent (16/18/6/11) HPV vaccination of girls at age 12 combined with a temporary (i.e., 5-year) catch-up vaccination program for girls and women 12 to 24 years of age. We assumed this vaccination strategy would be combined with current cervical cancer screening practices. Moreover, we assumed that current cervical cancer screening practices would not change with the introduction of HPV vaccination.

The efficacy of the vaccine strategy in preventing incident HPV infection (HPV 6/11 or 16/18) was assumed to be 90%. We assumed the prophylactic efficacy of the vaccine in preventing HPV-related diseases (i.e., HPV 6-, 11-, 16-, and 18-related CIN and genital warts) was 95.2% and 98.9%, respectively.[15] The duration of protection provided by vaccination was assumed to be lifelong, as was done in previous models.[16–18] We assumed that the natural course of acquired infection and disease is unaltered following vaccine failure or loss of vaccine-induced immunity. Because this is a prophylactic vaccine, we did not assume any therapeutic benefits when administered to persons infected with HPV.

We assumed that 70% of adolescents would receive a three-dose vaccine before they turned 12, similar to the coverage rates used in previous models.[17,19,20] Coverage was also assumed to increase linearly from 0% up to 70% during the first 5 years of the program (i.e., 14% in year 1, 28% in year 2, etc.) and remain at 70% thereafter. We assumed that the annual vaccine coverage for three doses of vaccine for the catch-up program in girls and women 12 to 24 who were previously unvaccinated would increase linearly from 0% up to 50% during the first 5 years (i.e., 10% in year 1, 20% of unvaccinated in year 2, etc.) and then drop to 0% per year after 5 years.

9.2.5 Economic Parameters

All costs were updated to 2005 U.S. dollars using the medical care component of the consumer price index. The direct medical costs for screening for and treatment of CIN, genital warts, and cervical cancer were based on administrative claims data and other sources.[21–23] We assumed the cost of the HPV vaccine for three doses and administration would be $360. All future costs and QALYs were discounted to present at a rate of 3% per year.

9.2.6 QoL Weight Parameters

One of the primary challenges with estimating QALYs in a CUA is estimating the QoL weights for the health states. When estimating a QoL weight, the range of potential values for a given health state are usually bounded by 0 and 1, where 1 corresponds to best imaginable health and 0 corresponds to death. Data for measuring the QoL weights (i.e., health utilities) can be obtained through a variety of approaches[24–26] and is discussed in detail in Chapter 11 on Patient Reported Outcomes.

For this CUA, we used estimates from studies reported in the literature. Table 9.1 summarizes the QoL weights used for the disease health states. We assumed females diagnosed with CIN1 and CIN2/3 would have quality weights of 0.91 and 0.87, respectively.[27,28] Males and females with genital warts were assumed to have a QoL weight of 0.91.[27] We assumed females with local and regional cervical cancer to have QoL weights of 0.76 and 0.67, respectively.[27] We derived a quality weight for invasive distant cancer of 0.48 from Gold et al.[29] using the 25th percentiles of female genital cancer weights. We assumed that the QoL weight for cervical cancer survivors after successful treatment would continue to be lower (i.e., 0.76) than that of healthy females.[30,31] The QoL weights for individuals harboring undiagnosed conditions of HPV, genital warts, CIN, and cervical cancer, and following successful treatment of CIN and genital warts, were assumed to be similar to those of individuals without HPV disease. We derived gender- and age-specific QoL weights from Gold et al.[29] to reflect the QoL impact of non-HPV related co-morbidities, which could potentially reduce the absolute gains in health utility achievable from preventing HPV disease.

9.2.7 Model Output: Epidemiologic

We used several measures to assess the epidemiologic impact of vaccination. Epidemiologic output included clinically diagnosed cases of CIN 1, CIN 2/3, invasive cervical cancer, and genital warts and cervical cancer-related deaths. These health states are shown in Figure 9.1.

TABLE 9.1
Health Utility Values

Health State	Estimate	Notation	Reference
Genital wart	0.91	*QGW*	28
CIN 1	0.91	*QCIN1*	27, 28
CIN 2	0.87	*QCIN2*	27, 28
CIN 3	0.87	*QCIN3*	27, 28
CIS	0.87	*QCIS*	27, 28
Localized cervical cancer treatment	0.76	*QLCC*	27
Regional cervical cancer treatment	0.67	*QRCC*	27
Distant cervical cancer treatment	0.48	*QDCC*	29
Cervical cancer survivor	0.76	*QCCS*	31
Healthy (age and gender specific)	0.70 to 0.93	*QH*	29

9.2.8 Model Output: Quality-Adjusted Life Years

As noted earlier, the QALY metric integrates all of the health benefits (i.e., quality and length of life) conferred by a healthcare technology into a single metric. To do this, the metric assigns QoL weights to each health state tracked in the model and integrates the sum of all of these adjusted health states over the planning horizon (0, 100). QoL weights for an individual experiencing a given condition were multiplied by the age and gender-specific QoL weight assigned to that individual. For example, if the life expectancy for a 55-year-old woman (age- and gender-specific QoL weight of 0.8) diagnosed with distant cervical cancer was 6 months (or 0.5 years), then the resulting number of undiscounted QALYs experienced would be valued at .19 (.5 x 0.48 x 0.8) QALYs. Hence, the QALY is calculated as the sum of the product of the expected time in the health state and the QoL experienced (i.e., QoL weight) over that time. The following equation shows the specific formula used to estimate QALYs.

$$QALY = \int_{o}^{100} \left[\sum_{i=1}^{17} QH_{fi} \begin{Bmatrix} NH_{fi} - \left(1 - QGW_{f}\right) NGW_{fi} - \left(1 - QCIN1\right) NCIN1_{i} - \left(1 - QCIN2\right) NCIN2_{i} - \\ \left(1 - QCIN3\right) NCIN3_{i} - \left(1 - QCIS\right) NCIS_{i} - \left(1 - QLCC\right) NLCC_{i} - \\ \left(1 - QRCC\right) NRCC_{i} - \left(1 - QDCC\right) NDCC_{i} - \left(1 - QCCS\right) NCCS_{i} \end{Bmatrix} + \sum_{i=1}^{17} QH_{mi} \left(NH_{mi} - \left(1 - QGW_{m}\right) NGW_{mi} \right) \right] e^{-0.03t} dt$$

Table 9.1 summarizes the health utilities assigned to each health state, the variable name for each health state represented in the equation, and the sources of the utility values. All variables in the equation beginning with N represent the total number of individuals with the associated conditions at time t. For example, NH represents the number of healthy individuals where f and m represent female and male respectively and i represents age. Hence, NHfi represents the number of females alive in age group i. NHmi represents the number of males alive in age group i. The model included 17 age groups.

It should be noted that we integrated the sum of quality-adjusted health states over the planning horizon (0, 100) because time is continuous. If time is treated as a discrete variable, as in many Markov models with fixed cycle length (e.g., 1 year), QALYs would be obtained as a sum of quality-adjusted health states from the present to 100 years.

Finally, we note that the age-specific QALY for females is reduced by time spent in diagnosed genital warts, CIN, and cancer states. Male age-specific QoL deteriorates by spending time with genital warts. All health states are multiplied by the age- and gender-specific weights to reflect the variation in QoL by age and gender groups.

9.2.9 Model Output: Economic

The economic output of interest from the model included total discounted costs and the incremental cost per QALY gained ratio. Both costs and QALYs were discounted at a 3% annual rate. We measured the cost-per-QALY ratio as the incremental cost difference between the two strategies divided by the incremental QALY difference between the two strategies.

9.2.10 Sensitivity Analyses

The focus of the sensitivity analyses reported here will be on the QoL weights and the influence changes in these weights have on the ICERs.

9.2.11 Epidemiologic Results

Table 9.2 summarizes some of the public health benefits of the vaccination strategy (i.e., vaccination of girls and women 12 to 24 years of age) relative to no vaccination in the United States. Specifically, Table 9.2 shows the cumulative additional cases of HPV-16/18/6/11-disease prevented in the United States with vaccination relative to no vaccination at years 10, 20, 50, 70, and 100 following the introduction of vaccination. For example, in row 2, column 4 of Table 9.2, the vaccination strategy compared with the no vaccination strategy is projected to reduce the number of cases of HPV 16/18-related cervical cancer by over 100,000 cases 50 years following the introduction of the HPV vaccine program in the U.S. population.

9.2.12 QALY Results

To estimate QALYs, we multiplied the amount of time spent in each of the disease states shown in Table 9.2 by the quality life weights in Table 9.1. Figure 9.2 shows

TABLE 9.2
Cumulative Additional Cases of HPV-16/18/6/11—Disease Prevented in the United States with Vaccination Relative to No Vaccination

	Years Since Vaccination Program Started				
	10	**20**	**50**	**70**	**100**
Cervical Cancer Deaths	0	479	19,701	41,458	76,544
Cervical Cancer	20	6,140	103,578	189,947	324,426
CIN 2/3	26,531	570,853	3,145,945	4,961,776	7,711,992
CIN1	8,533	189,860	900,595	1,378,583	2,097,669
Genital Warts	250,336	2,955,871	11,024,892	16,365,481	24,403,341

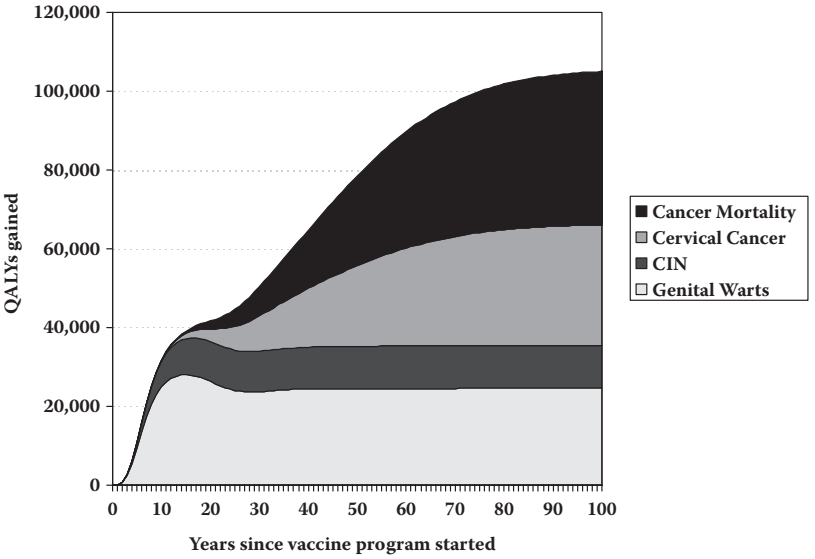

FIGURE 9.2 Undiscounted QALYs gained with vaccination over time.

the net QALYs gained (undiscounted) over time with vaccination relative to no vaccination by disease (health) state. The total QALY gained for the vaccination strategy would be estimated by calculating the area under the curve. Overall, prevention of genital warts accounted for 33% of the total QALYs gained over 100 years. In addition, prevention of cervical cancer deaths, cervical cancer cases, and CIN cases accounted for 29%, 25%, and 14% of the total QALYs gained over 100 years, respectively. Figure 9.3 shows the net discounted QALYs gained over time with vaccination relative to no vaccination by disease state. The total QALYs gained for the vaccination strategy would again be estimated by calculating the area under the curve. Overall, preventing genital warts accounted for 45% of the total QALYs gained over 100 years, which is higher than in the undiscounted analysis. This was because the discounted value of preventing the other HPV diseases was reduced in relative magnitude as these diseases increased their relative proportion of the total QALYs gained further out in time when compounded discounting had a greater impact in reducing their contribution to total QALYs gained. Cervical cancer deaths, cervical cancer cases, and CIN cases thus accounted for only 20%, 19%, and 17% of the total discounted QALYs gained over 100 years, respectively.

9.2.13 Cost-Effectiveness Results

To assess the cost-effectiveness of the vaccination strategy, we estimated the total discounted costs and effects (i.e., QALYs) accrued over a 100-year period for each strategy. These total costs and QALYs are shown in columns 2 and 3, respectively, in Table 9.3. Next, we calculated the incremental cost incurred to achieve an incremental gain in benefit with vaccination relative to no vaccination. These incremental

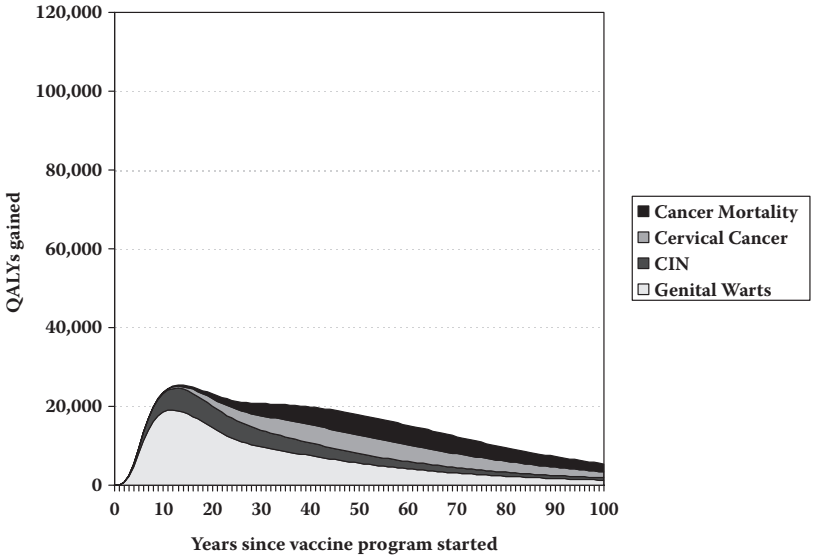

FIGURE 9.3 Discounted QALYs gained with vaccination over time.

TABLE 9.3
Cost-Effectiveness Analysis of an HPV Vaccination Program that Targets Girls and Women under the Age of 25 Relative to No Vaccination in the United States

Strategy	Total Costs (1,000s)	Total QALYs (1,000s)	ΔCosts (1,000s)	ΔQALYs (1,000s)	ΔCosts / ΔQALYs (ICER)
No Vaccine (screening only)	$174,340,679	6,476,910			
Quadrivalent Vaccine (12 to 24 girls and women)	$179,818,630	6,478,399	$5,477,951	1,489	$3,680

Note: Δ = the incremental difference between strategies.

costs and effects are shown in columns 4 and 5. Note that the total discounted QALYs gained over 100 years in the U.S. population (i.e., 1,489,000) were calculated by estimating the area under the curve in Figure 9.3. The final column shows the ratio of the incremental costs to incremental QALYs gained (i.e., the ICER). The ICER for vaccination was $3,680 per QALY gained.

We also explored a variety of sensitivity analyses where we varied the QoL weights assigned to the health states. We have summarized the results of these sensitivity analyses in Table 9.4. For example, in row 1, column 3, of Table 9.4, we

TABLE 9.4
Summary of Incremental Cost-Effectiveness Ratios for Sensitivity Analyses

Input Variable	ΔQALYs (1,000s)	ICER
Increase quality of life weight decrement by 50%	2,084	$2,629
Reference case	1,489	$3,680
Decrease quality of life weight decrement by 50%	893	$6,132
No protection against HPV types 6/11 (e.g., no genital wart benefit)	895	$10,103
No quality of life weight decrement (i.e., life years gained)	298	$18,387

show the ICER decreases to $2,629 per QALY gained when we assumed the decrement in the QoL weights for the disease states were 50% greater. The reason for the decrease in the ICER is evident from column 2, which shows that an additional 595,000 QALYs would be gained relative to the reference case if we assumed the decrement in the QoL weights for the disease states was 50% greater. However, when we assumed the decrement in the QoL weights for the disease states was 50% less, the ICER increased to $6,132 per QALY gained (row 3). Again, column 2 shows fewer QALYs would be gained relative to the reference case if the QoL weights for the disease states were 50% less.

We also examined two other scenarios where we partially or completely eliminated the QoL benefits of the vaccine. In one scenario, we eliminated any benefits associated with protecting against HPV 6/11 infection and disease. The resulting ICER under this scenario increased to $10,103 per QALY gained. This increase in the ICER was attributable to two factors. First, the number of QALYs gained relative to the reference case was less. Second, the total cost of the vaccination strategy was significantly higher than the total cost of the vaccination strategy in the reference case because the reduction in the costs of preventing genital warts was eliminated from this scenario. Finally, we examined a scenario where no QoL benefits would be realized by preventing CIN, genital warts, and cancer (i.e., all of the benefits were due to life extension only, with no improvement in QoL). The resulting ICER increased to $18,387 per QALY gained. Again, the QALY benefits gained in this scenario (i.e., 298,000) were significantly less than the reference case. In fact, these QALYs gained represent only survival gains (i.e., life years gained).

9.3 COMMENTARY

The primary research question this case study aimed to answer was, "What is the cost-effectiveness of a quadrivalent HPV vaccination strategy that targets girls and women 12 to 24 years of age relative to a strategy of no vaccination in the United States from a healthcare system perspective over a 100-year analytic horizon?" We found that for the reference case analysis the ICER was $3,680 per QALY gained.

The second research question this case study aimed to answer was, "Is a quadrivalent HPV vaccination strategy that targets girls and women 12 to 24 years of age

relative to a strategy of no vaccination in the United States cost effective?" Based on thresholds used by cost-effectiveness analyses in the United States, a quadrivalent HPV vaccine would be considered cost-effective as the ICER is less than $50,000 per QALY gained.[3,4] Similarly, based on threshold ICERs set by NICE in the UK and the WHO, quadrivalent HPV vaccination would also be considered cost-effective from these perspectives. Finally, if one were to compare the ICER to ICERs of other commonly accepted medical technologies using the Cost-Effectiveness Analysis Registry at Tufts Medical Center, quadrivalent HPV vaccination would be considered cost effective.[6] For example, the ICER for dialysis in end-state renal disease (ESRD) in the United States ranges from $50,000 to $100,000 per QALY gained.[32] Given that Medicare reimburses for dialysis for ESRD in the United States, HPV vaccination would represent a good value relative to dialysis for ESRD. Similar conclusions to these have been reached within U.S. policy-making contexts. For instance, the ACIP at the CDC concluded that, based on CEA models from industry, academia, and the government, vaccination of 9 to 26-year-old females with the quadrivalent vaccine was a solid investment, with ICERs within an acceptable range of cost effectiveness.[7] All of the cost-effectiveness models reviewed by the ACIP in this deliberation reported incremental cost per QALY gained ratios.[9,18,–20,33]

Thus, one of the primary benefits of using CUA is the ability to provide decision-makers with a common yardstick from which to assess the relative value of a healthcare technology. If we had examined cost per cervical cancer case avoided in this CUA, we would not have been able to compare the ICER with the ICER of healthcare technologies that do not prevent or treat cervical cancer. In fact, this very issue was subsequently raised at the ACIP when evaluating the cost-effectiveness of a rotavirus vaccine.[34] The cost-effectiveness analysis presented to the ACIP only reported ICERs that used cases of rotavirus avoided and life years gained in the denominator because QoL weights were not available to account for the childhood morbidity associated with rotavirus. The ACIP noted that these metrics limited their ability to assess the value of the rotavirus vaccine relative to other vaccines they had deemed as being cost effective. As a result, the ACIP recommended that QALYs be incorporated into the cost-effectiveness analysis in order to better assess the acceptability of the cost-effectiveness of rotavirus vaccination.[34]

Another benefit of CUA is that it allows for all the benefits of a healthcare technology to be considered. For example, we showed the impact of not accounting for QoL benefits in the sensitivity analyses. In particular, the ICER increased almost fivefold to $18,387 per QALY gained when we eliminated the QoL benefits of preventing genital warts, CIN, and cervical cancer. As shown in Figure 9.2 and Figure 9.3, these quality benefits exceeded the mortality benefits. In addition, these QoL benefits were realized sooner in the population than were the survival benefits. Hence, using survival gains as a metric for evaluating HPV vaccines significantly undervalues the benefits of the vaccine. For other disease areas such as arthritis and migraine, QoL decrements would account for virtually the entire health benefits associated with any intervention and an analysis of life-years gained would be inappropriate.

Given the ability of CUA to facilitate comparing the relative value of differing healthcare technologies, CUA has enjoyed significant growth as a preferred method

of CEA in the field. The CUA is not without its limitations. In particular, many over the years have been critical of using the QALY as the denominator in the ICER because either the metric is too complex and not pragmatic or not complex enough to accurately characterize how individuals value the QoL weights.[35] As a result, others have proposed alternative metrics. However few CEAs have adopted these other metrics. Hence, the literature on CUA with QALYs continues to grow and facilitate a language from which to compare the relative value of different healthcare technologies.

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