Chapter 18: Public health policy for cervical cancer prevention: The role of decision science, economic evaluation, and mathematical modeling

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Received 4 April 2006; accepted 15 May 2006

Abstract

Several factors are changing the landscape of cervical cancer control, including a better understanding of the natural history of human papillomavirus (HPV), reliable assays for detecting high-risk HPV infections, and a soon to be available HPV-16/18 vaccine. There are important differences in the relevant policy questions for different settings. By synthesizing and integrating the best available data, the use of modeling in a decision analytic framework can identify those factors most likely to influence outcomes, can guide the design of future clinical studies and operational research, can provide insight into the cost-effectiveness of different strategies, and can assist in early decision-making when considered with criteria such as equity, public preferences, and political and cultural constraints.

Keywords: Decision science; Economic evaluation; Mathematical modeling; HPV

1. Introduction

When making decisions we can either base choices on evidence and the explicit comparison of alternative strategies or we can use the intuitive opinions of experts. Decision science provides a quantitative framework for evaluating available evidence and uses explicit models to synthesize data, acknowledge uncertainty, and extrapolate from specific studies [1].

Several innovations are changing the landscape for cervical cancer prevention and control, with important differences in the most relevant policy questions for different settings. In countries with existing screening programs, pressing questions center around the optimal use of HPV-DNA testing, reducing disparities, and defining synergies between screening and vaccination. Important questions in low-resource settings include how to implement and sustain screening strategies with fewer technical and infrastructure requirements than required by conventional cytology-based programs, how to target the appropriate age groups for screening, and how to overcome the logistical barriers associated with delivering a three-dose vaccine during early adolescence. Key questions include: what is the coverage that could realistically be achieved with screening between ages 35 and 40 versus vaccination at ages 10–12? Will both boys and girls need to be vaccinated? Is there a combined screening/vaccination strategy that could be cost-effective or will decision makers need to choose between the two?

No single empirical study can evaluate all possible strategies to inform these complex policy questions. By integrating the best biologic, epidemiologic, economic, and behavioral data, the use of modeling in a decision analytic framework can assist in early decision-making, can highlight where better data are needed and identify those factors most likely to influence outcomes, can inform clinical study design and guide the conduct of operational research, and can provide insight into the potential cost-effectiveness of different strategies. Here we review the elements of cost-effectiveness analysis and identify the methodological issues most relev-
vant to upcoming policy questions in the cervical cancer field.

2. Decision analysis and cost-effectiveness analysis

Decision science offers an explicit, quantitative, and systematic approach to decision-making under uncertainty [1]. A collection of quantitative methods is used to guide the management of complex problems that involve competing choices, different perspectives, and trade-offs. The premise of a decision analytic approach is that all consequences of decisions should be identified, measured, and valued while also considering the uncertainty that exists about the outcomes at the time decisions are made.

A decision analysis is considered a cost-effectiveness analysis when it compares the relative health and economic consequences associated with different interventions. In a cost-effectiveness analysis, we are asking how much health improvement can be gained, dollar for dollar, compared to an alternative use of those resources. The implication is that resources should be used as efficiently as possible in order to maximize the health benefits to the population. The underlying principle guiding the valuation of resources is opportunity cost, which reflects competing societal demands for resources. Cost-effectiveness analysis takes a utilitarian approach to healthcare policy since it explores the maximization of aggregate population health. There are many additional criteria considered in priority setting, such as affordability, equity, public preferences, and the political and cultural consequences of decisions [2].

Results of cost-effectiveness analyses are summarized using a cost-effectiveness ratio. In this ratio, all health outcomes (compared to an alternative) are included in the denominator and all costs or changes in resource use (compared to an alternative) are included in the numerator. Cost-effectiveness analyses are always comparative, as the ratios evaluate the costs and benefits of each strategy relative to the next most effective strategy [3]. This means that the costs and clinical benefits associated with the intervention of interest should be compared to all other reasonable options. Several published guidelines advocate standard methods and assumptions to improve the quality and comparability of cost-effectiveness analyses [2–9], and several core principles are described briefly below.

2.1. Framework and perspective

The choice of perspective depends on the analytic goal and context of the decision, and dictates which costs and which health benefits to count and how to value them. A societal perspective incorporates all costs and all health effects regardless of who incurs the costs and who obtains the benefits, and is recommended for studies that inform the broad allocation of healthcare resources. Other perspectives, such as the payer perspective, may be more appropriate for specific local decisions.

2.2. Interventions

Interventions can be categorized along many dimensions [6,7]. For example, interventions to reduce cervical cancer mortality include primary prevention (vaccination), secondary prevention (screening), and therapy (treatment for invasive cancer). Interventions can include the provision of personal health services (services at the clinic or school level, district facility, or referral hospital) or be population-based (organized immunization or screening programs). Interventions may also include policy-related activities such as legislation (mandatory vaccination), measures to improve quality of care, and economic incentives such as taxes or subsidies. Finally, interventions differ in terms of their complexity and the intensity of demand they place on the health system. These dimensions are not mutually exclusive, and interventions might include combinations of features from different categories. An example might be the inclusion of several vaccination strategies that differ according to mode of operational delivery, age of vaccination, inclusion of boys, and intensity of recruitment.

The choice of interventions included in a cost-effectiveness analysis may vary between settings. For example, in a low-income country annual Pap screening is not a realistic option—rather, reasonable alternatives might include vaccination alone, screening three times per lifetime, and vaccination followed by a single lifetime screening between ages 35 and 40. The choice of the baseline comparator may also vary depending on both the setting and the objective of the analysis. When the baseline comparator is specified as the “null” (i.e., no intervention), as is often the case in analyses considering multiple new interventions, the incremental cost-effectiveness ratio that is calculated for the first intervention is sometimes referred to as an average cost-effectiveness ratio. In analyses intended for local decision-making, it may be useful to assess alternative strategies relative to the current standard of care. For example, in the US, the relevant baseline comparator for the question of “What will an HPV-16/18 vaccine add to our current cervical cancer program?” is current screening practice [10].

2.3. Health outcomes

Health units for measuring the population impact can be disease-specific clinical outcomes, such as cases of cancer prevented. Although such clinical outcomes are easily understood, a disadvantage is that results can only be compared to studies using the same outcomes. In order to compare ratios across different interventions and diseases, the denominator must be expressed in a common metric, such as life-expectancy, years of life lost (a measure of the impact of an adverse health event, calculated by subtracting the age at which death occurs from life expectancy at that age),
quality-adjusted life years (a unit for measuring the health gain associated with a clinical or public health intervention, calculated as the number of years of life saved adjusted for the quality of life during those years), or disability-adjusted life years (a unit for measuring the health lost because of a particular disease, calculated as the future years of disability-free life that are lost as the result of premature deaths or cases of disability occurring in a particular year) [2,3,5,7,8].

The fundamental distinction among various quality-adjusted measures is whether they describe a person’s state of health (i.e., health status) or ascertain a value for a state of health (i.e., utility) [3]. Preference measures reflect the fact that people with similar symptoms or levels of function may value that level of health differently. There is debate over how well health preferences are currently measured, particularly with respect to temporary health states experienced by women participating in screening programs (e.g., false positive results, work-up of abnormal cytology, diagnosis of HPV infection) and with diagnosis of sexually transmitted infections, where there is the added potential for social stigma [11]; more research is needed in this area.

2.4. Non-health outcomes

Non-health benefits not captured in traditional cost-effectiveness analyses range from a reduction in impoverishment from improving earning capacity, or reducing catastrophic out-of-pocket payments, to improving the probability of children remaining in school [2]. For example, preventing cervical cancer saves the lives of relatively young women who have crucial roles in caring for dependents and maintaining the stability of the household and the larger community. Although there is no consensus on how to measure and quantify non-health benefits for inclusion in a cost-effectiveness analysis, they should at least be identified.

2.5. Cost outcomes

The numerator of the cost-effectiveness ratio represents the difference in resources used when implementing one strategy compared to those used in the next best strategy (e.g., comparing resources used for HPV vaccination combined with screening to those used with vaccination alone).

For analyses conducted from a societal perspective, costs must reflect resource use, not only for the intervention itself, but also for the downstream events that follow. Key cost categories include: (1) direct healthcare costs (e.g., screening test, clinic visit, laboratory tests, specimen transport, subsequent healthcare visits for treatment, further tests and treatment); (2) direct non-healthcare costs (e.g., patient transportation costs, child or dependent care, time spent by family for caregiving); (3) patient time costs (e.g., the time spent by the patient receiving care); (4) programmatic costs (e.g., costs incurred at the administrative levels rather than the point of care delivery). The identification, measurement, and valuation of these resources are not always straightforward. For example, patient time is conventionally valued using wage rates, but this method underestimates the value of women’s time for those who either work in the informal sector or take care of the household and dependents [12]. Programmatic costs are rarely included in analyses because they are difficult to estimate, but may differ considerably between interventions. Finally, there are obvious data limitations, especially in poor countries: details such as specimen transport, road network density, and proportion of the population in rural areas are all rarely formally considered but may be very influential on intervention costs. Fig. 1 shows an example of screening cost components for selected countries in which many of these details were included, and highlights the importance of including non-medical costs. The striking difference in the types of costs between locations illustrates the potential importance of the local organization of healthcare, available infrastructure, travel distance required for screening, and economic conditions. These differences need to be considered in country-specific analyses.

2.5.1. Cost units

Costs should be presented in currency units that remove price inflation; additionally, for analyses intended to inform resource allocation and compare studies from multiple countries, costs should be expressed as US dollars or international dollars. Prices in local currency can be converted to US dollars using exchange rates or to international dollars using purchasing-power parity rates. While the former may reflect under- or overvaluation of the local currency they represent what is actually paid for locally-produced inputs [5]. Purchasing-power parity rates, in contrast, attempt to reflect what the local currency is worth in purchasing power, and therefore account for differences in price levels across countries. The exchange rate for domestic currency into international dollars is the amount of domestic currency required to purchase the same quantity of goods and services as US$ 1 could purchase in the US [3,5–7].

2.5.2. Discounting

Future costs and benefits should be discounted to their present values to reflect inherent uncertainty about the future and preferences for timing of consumption. For example, at a 3% discount rate, a cost of US$ 1 next year would be equivalent to US$ 0.97 today. Although there is consensus about the need for discounting costs, there is controversy about the discounting of benefits, the appropriate rate to use, and whether the rate should be constant [3,6–8,13]. Discounting may undervalue interventions for which the benefits appear long after the costs have been paid. For example, immunization against HPV-16/18 could prevent cervical cancer decades later and can appear less cost-effective if the health gain is heavily discounted during that interval. The implication of this is clearly shown in Fig. 2, which depicts the differential impact of discounting on screening as opposed to vaccination.
Fig. 1. Screening cost components shown for selected countries for two cervical cancer strategies expressed in 2000 international dollars. The height of each bar represents the total costs associated with the initial screening visit for HPV-DNA testing and cytology, while the colored regions within bars represent categories of costs. Direct medical costs are subdivided into those attributable to staff (dark blue), supplies (medium blue), and equipment and laboratory (light blue). Other costs include transportation costs (red) and the time associated with women traveling, waiting, and receiving care (yellow). When data were unavailable to disaggregate the direct medical costs, we placed these into a single category (green). The considerable variation in patient time and transport costs reflects differences in rural population and density, comprehensiveness of coverage by the primary clinic, wages, and/or difficulty in travel.

2.5.3. Other cost issues

Certain costs (aside from vaccine price) that are of particular relevance to vaccination strategies include costs of delivery strategies, costs attributable to vaccine wastage, and the costs of achieving incremental increases in coverage rates. There are no empirical data on any of these for a three-dose vaccine targeting adolescents. An additional important issue relates to how the rate of change in costs compares with the change in benefits as vaccination coverage increases or “scales-up”. Scale-up refers to the changes in an intervention’s effectiveness and costs as coverage is expanded to larger percentages of the eligible population. For some costs, economies of scale might be achieved (i.e., the per-person cost of delivering an intervention is reduced as coverage is increased) with, for example, bulk manufacturing and supply chain management. However, there may also be diseconomies of scale, such as increased costs of distribution and staffing in remote locations. The functional relationship between cost and scale is frequently ignored but is worthy of further empirical study [6,7,14].

3. Reporting the results of a cost-effectiveness analysis

Cost-effectiveness results are often displayed in the format of an efficiency curve, as shown in Fig. 3, where the lifetime costs and clinical benefits (discounted life expectancy on the left vertical axis, reduction in lifetime risk of cancer on the right vertical axis) of different screening strategies performed at different screening intervals are shown. Strategies lying on the efficiency curve dominate those lying to the right of the curve because they are more effective, and either cost less or have a more attractive cost-effectiveness ratio than the next best strategy. The slope between two strategies is steeper when the net gain in health per unit cost is greater.

In this example, strategies of screening with HPV-DNA testing once, twice, and three times per lifetime dominate other strategies [12]. The two and three times in a lifetime screening strategies are positioned higher on the curve—in this region of the curve the slope is steep, which signifies rapidly escalating clinical benefits for only modest increases in costs. The cost-effectiveness ratios associated with these screening strategies reflect this relationship in that they are two- to five-fold higher. Some strategies lie near the efficiency curve, where slight changes in direct medical costs or test performance would make them equally cost-effective as the strategies lying on the efficiency curve.

Analysts may also choose to present cost-effectiveness results in other formats. An advantage of using a tabular format is that a range of outcomes that different decision makers find helpful may be presented for each strategy. For example, these might include intermediate outcomes (e.g., cases of cancer prevented) and discounted and undiscounted results. The scale and consequences of a screening or vaccination strategy that is subject to limited monetary resources can be represented by expressing the results as the cost and effects of applying the intervention to a target population of 1 million.

Although certain outcomes cannot be captured in a cost-effectiveness ratio with current methods, analysts must begin...
to qualitatively identify results that could influence the comparative attractiveness of different interventions. These include identifying non-health benefits and the extent to which interventions differentially place demands on the health-system capacity.

4. Interpreting the results of a cost-effectiveness analysis

While interventions that improve health at a cost should ideally be compared with other interventions that compete for the same resources, there is no universal criterion that defines a threshold cost-effectiveness ratio, below which an intervention would be considered cost-effective. A commonly-cited rule of thumb is based on a report by the Commission on Macroeconomics and Health (CMH), and subsequent recommendations that interventions are “very cost-effective” and “cost-effective” if they have cost-effectiveness ratios less than the per capita GDP or three times the per capita GDP, respectively [6,15]. Because of the interaction between cost-effectiveness, disease burden, and available funds, the cost-effectiveness ratio alone is an inadequate guide to priority setting; additional criteria such as affordability, distributional impacts and equity considerations, capacity to deliver interventions, and public preferences can often be more influential [2].

Therefore, provided there is acknowledgement that cost-effectiveness is only one relevant input for policy decisions, and when comparable methods are used to conduct analyses, using the per capita GDP as a rough indicator of monetary resource constraints is not unreasonable. On the single dimension of cost-effectiveness, having some threshold range (e.g., 0.5–3 times the per capita GDP) allows loose classification of
Fig. 3. An example of an efficiency curve derived from an analysis of potential screening strategies with costs derived for South Africa and including different number of lifetime screens (1 time at age 35; 2 times at ages 35 and 40; or 3 times at ages 35, 40, and 45): the lifetime costs (horizontal axis) and clinical benefits (discounted life expectancy on the left vertical axis, reduction in lifetime risk of cervical cancer on the right vertical axis) of different screening strategies. One-visit strategy refers to testing with either HPV or VIA, followed by immediate treatment if screen positive. Two-visit strategy refers to HPV testing followed by treatment if HPV-positive. Three-visit strategy refers to Pap testing followed by colposcopy-directed biopsy, and treatment when diagnosed with pre-invasive or invasive lesions. For simplicity, some of the dominated alternatives have been left out of the illustration; full details can be found in Ref. [12].

interventions into broad categories of very cost-effective, not cost-effective, and potentially cost-effective. It also allows us to conduct uncertainty analyses that identify the probability that a cost-effectiveness ratio is below some threshold.

For an HPV-16/18 vaccination strategy in particular, there may indeed be a lower “threshold ratio” required to compete for scarce vaccination resources if the ratios associated with existing vaccines (e.g., childhood immunization) being used are much lower than the GDP rule of thumb cited above. In the past, most cost-effectiveness analyses for cervical cancer screening have concentrated on questions of “technical efficiency”, meaning that given several competing options for cervical cancer screening, which are the most cost-effective. When cost-effectiveness analysis is used to inform “allocative efficiency”, the requirement to consider the cost/benefit profile relative to other investments in other disease areas is more prominent. Therefore, in addition to comparing screening and vaccination approaches within the cervical cancer paradigm, how the cost-effectiveness of an HPV vaccine compares with the cost-effectiveness of other well-accepted vaccinations will be critical.

5. Use of models

Models can be classified along several dimensions: according to the structure used for events that occur over time (e.g., decision trees, state transition models); whether they are open or closed and according to the nature of the target population (e.g., a longitudinal cohort model, cross-sectional population model); by the method of calculation (e.g., deterministic, stochastic); and whether they reflect the transmission dynamics of infection [3,16,17]. Models utilize a wide range of approaches to calibrate to data, estimate uncertain or unknown parameters, and evaluate uncertainty and variability. As a general rule, all models involve trade-offs. For example, including more detail means that more parameter values are required and, consequently, the model becomes more complicated and challenging to analyze [16,18].

Both models of “transmission dynamics of infection” and “disease simulation models” categorize individuals into mutually-exclusive health states. Movement between health states can be described by a system of equations, which depends upon the mathematical framework. Difference equations represent discrete jumps in time, where the state of the system at the next time-step depends upon the current system and terms reflecting movement between categories over the entire interval. In contrast, differential equation models, either ordinary or partial, represent systems in continuous time, though complex models of this variety are often analyzed using discrete approximations.

Examples of two model schematics are shown in Fig. 4. Diagrams are often developed to highlight the most influential model parameters and, by making assumptions explicit, allow healthy debate and discourse over alternative model structures, parameters, and assumptions.

In state-transition models used to assess cervical cancer prevention strategies, important factors influencing the probabilities governing movement between health states include age, sexual risk, HPV type, exposure to screening, and probability of immunity following HPV infection. While in a disease simulation model, such as the type used to assess the cost-effectiveness of screening, the probability of HPV acquisition is permitted to depend on age and a general sexual risk category; in a transmission model, the probability of an individual acquiring an infection is modeled as dependent on the detailed sexual contact patterns of that individual and the distribution of the infection within the population at that
specific time [19–21]. Because interventions that affect the individual have consequences for the risks of infection in the rest of the population, models that describe the transmission dynamics of infection are necessary to estimate the impact of herd immunity, explore the relative value of vaccinating boys in addition to girls, and explore the impact of sexual mixing patterns on the projected age-specific HPV prevalence following vaccination.

Many of the parameters required for transmission models are largely unknown for HPV types other than HPV-16 [22]. Even for HPV-16, the data are limited for transmission rates in men and women and for detailed sexual behavior stratified by variables such as gender, age, and other risks. Since so many variables are unknown, simplifying assumptions are unavoidable. Transmission models that only include HPV-16, or only HPV-16 and -18, can provide estimates of the reduction in 16/18-associated cervical cancer but are more limited in terms of exploring detailed questions around the natural history, outcome, and resource use associated with non-16/18 types.

A static state-transition model is well suited to simulate chronic disease with multiple stages over relatively long time periods, can include considerable detail on different screening and treatment strategies, and can accommodate the detailed cost measures associated with each health state [16,23,24]. Most published cervical cancer screening models are state-transition models that are “closed,” in that no one enters or exits the cohort at any time during the simulation, although these models may also be open, allowing people to enter or exit over time. Advantages of closed models are that they are transparent, can easily accommodate probabilistic uncertainty analysis, and are efficient in terms of computational intensity. However, “open” population-based models and first-order Monte Carlo simulation allow for more flexibility in capturing multiple dimensions of heterogeneity (e.g., type-specific HPV, individual-based risk factors such as parity, smoking, etc.), thereby reflecting both variability and uncertainty and permitting the risk of future events to depend on one or more prior events [25].

As models evolve in complexity, the requirement for parameter values quickly multiplies and input values will almost certainly never be available for all parameters. Calibration techniques that fit model output to epidemiologic data on age-related prevalence of type-specific HPV, age-related incidence of cervical intraepithelial neoplasia (CIN) and inva-
sive cancer, and the distribution of HPV types within CIN and cancer, are increasingly being used [25].

A critical part of any decision analysis is to evaluate the uncertainty in the model structure, parameter estimates, and assumptions [3,16,18]. Validation of a model requires a demonstration that the output of the model is consistent with known facts about the disease. This process will include simple tests as well as more complex calibration exercises, in which statistical methods are used to maximize the likelihood function for observed data given a set of parameter values. Predictive validity refers to whether a model produces outputs that are consistent with observations independent of data used to calibrate the model.

Statistical issues in cost-effectiveness studies are different from those that arise in experiments or other data analyses. Rather than testing hypotheses using traditional statistical significance as a criterion, model-based evaluation studies aim to portray the scope and nature of the uncertainties that surround the estimates of costs, benefits, and cost-effectiveness ratios. The most common way to evaluate the stability of conclusions over a range of parameter estimates and structural assumptions is to conduct sensitivity analyses. The range of values used for a sensitivity analysis can be based on statistical variation for point estimates or on probability distributions. In a sensitivity analysis, some critical component in the calculation is varied over a plausible range and the cost-effectiveness ratio is recalculated. The resulting difference in the ratio provides some indication of how sensitive the results might be to a change in that parameter.

The process described above focuses on discerning the influence of a particular, limited set of parameters, whereas to understand the uncertainty, all parameters should be varied simultaneously. Probabilistic sampling assumes some knowledge of the distributions surrounding a model’s input parameters and takes random draws from these distributions to calculate outcome variables. Probabilistic sensitivity analysis can be performed using a Markov model analyzed as a cohort simulation, and using recently-developed techniques, can be performed on a Markov model analyzed as a first-order Monte Carlo simulation [26,27]. An important caveat is that data for estimating probability distributions around mean parameter estimates are seldom available in low- and middle-income countries.

6. Conclusion

Evaluating the effectiveness of a public health prevention program is complex, particularly when the course from infection to disease spans multiple decades, when new activities are building upon existing interventions, and when resource constraints limit the range of reasonable choices. Decision science and cost-effectiveness analyses offer important tools that can help to address key cervical cancer policy questions relating to screening and vaccination.

Disclosed potential conflicts of interest

GPG: Consultant (GlaxoSmithKline, Merck and Co., Inc., Sanofi-Pasteur MSD, Sanofi-Pasteur); Research Grants (GlaxoSmithKline)

Acknowledgments

Dr. Goldie is supported in part by the US National Cancer Institute (grant #R01 CA093435) and The Bill and Melinda Gates Foundation (grant #30505). Mr. Goldhaber-Fiebert is supported in part by a National Science Foundation Graduate Research Fellowship. We gratefully acknowledge the valuable contributions of Steven Sweet and Meredith Holtan of the Harvard School of Public Health, Boston, MA, for their outstanding technical assistance.

References


