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CHAPTER 10

A public health approach to cervical cancer control: Considerations of screening and vaccination strategies

Sue Goldie

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HPV DNA testing;
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Abstract Cervical cancer remains a leading cause of cancer death among women living in low-resource settings. In the last 3 decades, cytologic screening has — in theory — been available and yet more than 6 million women have died of this preventable disease. The necessary resources, infrastructure, and technological expertise, together with the need for repeated screenings at regular intervals, make cytologic screening difficult to implement in poor countries. As noncytologic approaches for the detection of HPV, simple visual screening methods for anogenital lesions caused by HPV, and the availability of an HPV-16/18 vaccine will enhance the linkage between screening and treatment, multiple factors will need to be considered when designing new, or modifying existing prevention strategies. Country-specific decisions regarding the best strategy for cervical cancer control will need to rely on data from many sources and take into account complex epidemiologic, economic, social, political, and cultural factors, and be made despite uncertainty and incomplete information. A rigorous decision analytic approach using computer-based modeling methods enables linkage of the knowledge gained from empirical studies to real-world situations. This chapter provides an introduction to these methods, reviews lessons learned from cost-effectiveness analyses of cervical cancer screening in developed and developing countries, and emphasizes important qualitative themes to consider in designing cervical cancer prevention policies.

1. Introduction

Cervical cancer remains a leading cause of death among women living in low-resource settings [1]. Moreover, affected women die at a younger age than those with almost any other cancer — a particularly devastating reality in developing countries where women aged between 30 and 50 years are critical to social and economic stability. Unlike most cancers, cervical cancer is preventable through cytologic screening programs that detect and treat precancerous lesions. In countries that have been able to achieve broad screening coverage at frequent intervals, mortality from cervical cancer has decreased considerably. In most resource poor settings, however, cytologic screening has proven diffi-

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cult to implement and sustain [2], in large part because this form of screening relies on highly trained cytotechnologists, high-quality laboratories, and an infrastructure to support up to 3 visits for screening, colposcopic evaluation of abnormalities, and treatment.

Several factors are changing the landscape for cervical cancer control. First, the availability of reliable assays for the detection of the presence of HPV has resulted in the successful completion of numerous studies, and most have documented the superior performance of these assays in detecting precancerous lesions compared with a single cytology test. Second, recent studies suggest that alternate screening strategies that use HPV DNA testing or simple visual screening methods may be more practical in many regions of the world [3–6]. Third, highly effective vaccines that prevent infection with 2 high-risk HPV types (HPV-16 and HPV-18) are likely to be available for clinical use in the very near future [7,8]. These factors will obviously need to be carefully considered in the design of cervical cancer prevention strategies, but there are policy differences between developed and developing countries.

In countries with existing screening programs the most relevant policy issues center around the optimal use of HPV DNA testing within the context of cytology-based programs; targeting programs to reduce disparities between groups seeking screening and treatment; improving the accuracy of screening tests to prevent unnecessary treatment and testing of women; and identifying the ways to use screening and vaccination together.

Among the most important issues to consider in low-resource settings are the cost-effectiveness of feasible alternatives to conventional cytology, such as visual screening methods and HPV DNA testing; the design and implementation of screening strategies that can be accommodated with less infrastructure or low technology alternatives; and mechanisms to target the appropriate age group for screening. In anticipation of the availability of an HPV-16/18 vaccine, additional questions need to be addressed: for example, how will countries overcome the logistical barriers associated with delivering a 3-dose vaccine during early adolescence, and is there a synergistic combination of screening and vaccination that is likely to be cost-effective, or should decision makers invest in one approach?

Evaluating the "real-world effectiveness" of a public health prevention program is complex, particularly in countries facing resource constraints, and particularly when the course of infection to disease spans multiple decades, as it does with HPV infection and cervical cancer. Determining the optimal screening policy requires consideration of:

- relative performance and costs of different screening tests;
- tradeoffs between test sensitivity and specificity;
- attributes of different tests that might facilitate uptake (e.g., self-sampling);
- alternative options to manage abnormal results;
- effectiveness of different treatment options.

Similarly, exploring the potential impact of a type-specific HPV vaccine in any specific world region requires a number of factors to be considered. Among these are:

- the age-specific incidence of HPV infection;
- vaccine efficacy in preventing HPV infection;
- achievable coverage of the appropriate population;
- viral heterogeneity and heterogeneity of response durability to the vaccine;
- risk of viral replacement with HPV types not targeted by the vaccine.

As no clinical trial or single longitudinal cohort study will be able to consider all of these factors and assess all possible strategies in all populations, public health decision making in the setting of incomplete information is unavoidable. A decision analytic approach using computer-based modeling methods provides a way to formally integrate many different types of data (e.g., biologic, epidemiologic, clinical, and economic), extrapolate costs and effects beyond the time horizon of a single clinical study, and compare multiple potential strategies targeting different points in the disease course. These methods provide a rigorous approach to linking the knowledge gained from empirical studies to real-world situations. In addition to guiding a decision process, the methods can help identify the most important factors that should govern a decision, provide insight into how that decision might change if values of key parameters are changed, and assist in prioritizing future data collection.

2. Decision analysis and cost-effectiveness analysis

Decision analysis as a discipline offers an explicit, quantitative, and systematic approach to decision making under uncertainty [9]. The field encompasses a collection of quantitative methods that have been developed to guide the management of complex problems requiring simultaneous consideration of multiple competing choices, different perspectives, and inevitable tradeoffs. Inherent in a decision analytic approach is the requirement to identify, measure, and value the outcomes or consequences of decisions, and to use methods to de-

scribe the uncertainty about these outcomes at the time when decisions are made.

Decision analyses that formally compare the relationships between the health and economic consequences of proposed public health care interventions are known as cost-effectiveness analyses. In a cost-effectiveness analysis we are asking how much health improvement can be gained, dollar for dollar, compared with an alternative use of those resources. The application of these methods to policy choices does not imply that less money should be spent; rather, it implies that resources should be used as efficiently as possible to maximize the health benefits to the population. The quality and comparability of cost-effectiveness analyses has improved in recent years, in large part owing to the availability of guidelines that provide consistent recommendations for standardized methodology and assumptions [10–16].

Results of cost-effectiveness analyses are summarized using a cost-effectiveness ratio. In a cost-effectiveness ratio, all health outcomes (compared with an alternative) are included in the denominator, and all costs or changes in resource use (compared with an alternative) are included in the numerator. Cost-effectiveness analyses are always incremental, with the ratios comparing the costs and benefits of each strategy to the next most effective strategy. This means that the costs and clinical benefits associated with the intervention of interest should be compared not only with existing practice but also with all other reasonable options. For example, a cost-effectiveness analysis of type-specific HPV vaccination will need to consider the *incremental* costs and *incremental* benefits associated with vaccination in comparison to all relevant screening options with different technologies and at different frequencies, and in comparison to different combinations of screening and vaccination [10]:

$$\frac{\text{(Costs of Vaccination and Screening} - \text{Costs of Vaccination Only)}}{\text{(Outcomes of Vaccination and Screening} - \text{Outcomes of Vaccination Only)}}$$

In the denominator of the cost-effectiveness ratio the choice of health units chosen to measure the impact on the population may vary. For example, health outcomes may be expressed as number of clinical events (e.g., cases of precancerous lesions detected), intermediate outcomes (e.g., cases of cervical cancer or deaths prevented), or long-term outcomes (e.g., life expectancy). However, for analyses intended to inform resource allocation and health policy decisions, it is necessary to compare ratios across different studies, types of interventions, and diseases and conditions. Therefore, the denominator must be expressed in a common metric, i.e., general life expectancy, quality-adjusted life years (QALY), or disability-adjusted life years (DALY) [10,12,13,15], using the following definitions for QALY and DALY:

- a QALY is a unit for measuring the *health gain* associated with a clinical or public health intervention, and is calculated as the number of years of life saved and adjusted for the quality of life during those years;
- a DALY is a unit for measuring the *health lost* because of a particular disease, and is calculated as the future years of disability-free life that will be lost as the result of the premature cases of death or disability occurring in a particular year.

The numerator of the cost-effectiveness ratio represents the difference in resource use resulting from implementation of a specific strategy (e.g., HPV vaccination combined with screening) compared with the next best strategy (e.g., HPV vaccination only). The choice of currency units for measuring costs may vary, although they should be expressed in constant dollars (e.g., US $2000) and discounted to the present value. For further reading on these topics we refer the reader to several excellent sources [10–13,16]. The numerator takes into account cost components, cost units, and discounting:

- **Cost components:** Costs should include all resources used on downstream events (e.g., follow-up of women with high-grade lesions) as well as resources needed to deliver the intervention (e.g., costs of screening). A societal perspective is recommended for analyses intended to inform resource allocation, which means that all costs are included regardless of where they accrue. The relevant cost categories include:
  - *direct health care costs* (e.g., screening test; clinic visit; laboratory tests; specimen transport; subsequent health care visits for treatment; further tests; and treatment);
  - *direct non-health care costs* (e.g., child care costs for a mother in treatment; transport costs for treatment; and time spent by family and friends for care giving);
  - *time costs* (e.g., time spent by the patient pursuing and receiving care). The time spent in treatment should be evaluated using wages if applicable, but also allowing for unpaid work such as child care.
- **Cost units:** For analyses intended to inform resource allocation and compare studies from multiple countries, costs should be expressed in 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 underevaluation or overvaluation of the local currency, they do represent what is actually paid for locally produced inputs [12]. Purchasing-power parity rates, in contrast, attempt to say what 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 reflects the amount of domestic currency required to purchase the same quantity of goods and services as $1 could purchase in the United States. For further reading on the choice of cost metrics we refer the reader to several sources [10,12,13].

- **Discounting:** Discounting refers to the standard practice in economic evaluations of converting future costs and benefits into their equivalent present values. For example, at a 3% discount rate, a cost of US $1 next year would be equivalent to US $0.97 today, and a cost of US $1 in 10 years' time would be equivalent to US $0.74 today. The discounting procedure reflects inherent uncertainty about the future and preferences for timing consumption. Although there is consensus about the need for discounting in cost-effectiveness analysis, there is controversy about the appropriate rate to use, whether it needs to be constant, and whether benefits and costs should be discounted at the same rate. Although 3% is often recommended as the base case [10,12,14,15], analysts are encouraged to present results using different rates in sensitivity analyses.

There is no universal criterion that defines a threshold cost-effectiveness ratio, above which an intervention would not be considered cost-effective and below which it would be considered cost-effective. One commonly used rule of thumb is based on a report by the Commission on Macroeconomics and Health, which suggested that interventions are “very cost-effective” if they have a cost-effectiveness ratio less than the per capita gross domestic product (GDP), or “cost-effective” if ratios are less than 3 times the per capita GDP [17,18]. There are many criteria relevant for priority setting in health aside from cost-effectiveness [19], such as affordability, equity (equal treatment for those in equal circumstances or prioritizing the worse off) and societal preferences [12].

3. Cost-effectiveness of cervical cancer screening

3.1. Countries with existing screening

Most published cost-effectiveness analyses of population-based cervical cancer screening performed in the last 2 decades focused on high-income countries and have addressed issues such as screening interval; ages for starting and stopping screening; ways to integrate HPV DNA testing into cytology-based screening programs (e. g., as triage for equivocal cytology results) or use it as a primary screening test for women older than 30 years; and assessment of national clinical guidelines. In general, findings have been consistent among studies [20–37].

The cost-effectiveness of screening in the general population becomes increasingly less favorable as programs are intensified by shortening the screening interval. There is very little benefit, and there are potentially harmful consequences, in beginning screening at too early an age (e.g., prior to 3 years after the beginning of sexual activity). Analyses comparing frequent cytologic screening with new screening strategies using tests with higher sensitivity (e.g., HPV DNA testing) reported unfavorable cost-effectiveness results when screening frequency was not modified. These studies, however, consistently found that HPV DNA testing was very cost-effective when used (1) as a triage for equivocal results as part of a 2- or 3-year screening frequency, and (2) in women older than 30 years as part of a 3- or 4-year screening frequency. Although many analyses found that extending the age range to the very young and/or the very old was less cost-effective, for certain women in high-risk groups, including older uninsured women who have never been screened, screening for cervical cancer at older ages was very cost-effective.

3.2. Countries without existing screening

There are few published studies that assess screening in developing countries [38–44]. The analyses conducted in low-income countries have focused on assessing the cost-effectiveness of an expanded set of strategies that included alternatives to conventional cytologic screening. In one of the first modeling evaluations of cervical cancer screening programs in developing regions, Sherlaw-Johnson, Gallivan, and Jenkins [43] report that the most efficient use of resources would be to focus screening efforts using cytology and HPV testing on women aged between 30 and 59 years at least once per lifetime to reduce the lifetime risk of cervical

cancer by up to 30%. Results using data from Thailand and South Africa, reported qualitatively similar results [39,41]. Most early analyses did not include programmatic costs and focused on a single country, limiting the generalizability of key findings.

Recently, however, investigators conducted a comprehensive assessment of the cost-effectiveness of cervical cancer screening strategies in 5 countries with differing epidemiological profiles but where conventional cytology screening programs had not been sustainable [40]. Costs were assessed using primary and secondary data, and included direct medical, time, and programmatic costs. To facilitate comparison between studies a series of standardized assumptions were agreed upon by an expert panel with representation from all 5 countries. Strategies differed by initial screening test; targeted age of screening; number of clinic visits required (1, 2, or 3); and follow-up protocols. Specific tests included visual inspection with acetic acid (VIA), cervical cytologic assessment, and HPV DNA testing. *Three-visit strategies*, the standard of care in most developed countries, included an initial screening test, a diagnostic work-up incorporating colposcopy and biopsy in women with positive results, and treatment of cervical intraepithelial neoplasia (CIN). *Two-visit strategies* incorporated initial screening followed by treatment, without evaluation by colposcopy, of all screen-positive women. *One-visit strategies*, (i.e., "screen and treat") incorporated immediate treatment in screen-positive women. Outcomes included lifetime risk of cancer, years of life saved (YLS), and lifetime costs (in international dollars).

In all 5 countries, the lifetime cancer risk was found to be reduced by approximately 25% with a single lifetime screening of women aged between 35 and 40 years and consisting of either a 1-visit VIA or a 2-visit HPV testing; and it was found to be reduced by nearly 50% with strategies targeting women 2 or 3 times per lifetime. Although the mean per-woman lifetime costs varied considerably, strategies were identified in all 5 countries that were very cost-effective relative to their GDP. Cost-effectiveness was most sensitive to loss to follow-up, targeted screening age, proportion of the female population covered, and cost of care for invasive cervical cancer.

To place the results into the context of other well-accepted public health interventions, the authors translated the cost-effectiveness ratios to an expression of the percentage of each country's GDP. They found that single lifetime screening strategies were as cost-effective as hepatitis B immunization in India, second-line treatment for tuberculosis in Peru, and malaria prevention with bed nets in Kenya [40].

Countries that opt for screening should decide on the basis of their own relative resources and preferences whether their setting is better suited for HPV testing or VIA. Cost-effectiveness analyses provide only one type of input into policy and are most useful for their qualitative insight. For a very poor country with only lower-level clinical providers, no laboratory infrastructure, and very scarce monetary resources, visual screening methods may be the most feasible option. On the other hand, for countries with some ability for centralized processing of laboratory tests, even if they have a low-income economy, HPV DNA testing may be more attractive. When new HPV DNA tests become available, less costly than the current assays and able to provide results within a few hours, the cost-effectiveness of HPV DNA testing will be even more favorable. For countries with an interest in combined vaccination and screening approaches, HPV DNA testing will likely be preferred. The additional information that could be obtained from HPV DNA would facilitate the surveillance of type distribution in partially-vaccinated populations.

3.3. Main themes from cost-effectiveness analyses of screening in settings with existing screening programs

- The cost-effectiveness of screening in the general population becomes increasingly less favorable as programs are intensified by screening more frequently than every 2 to 3 years, and/or by aggressively following equivocal or low-grade cytological abnormalities;
- Strategies that employ screening tests with higher sensitivity than conventional Papanicolaou (Pap) smears (e.g., liquid-based cytology with reflex HPV testing, enhanced cytology with computer-assisted imaging, and primary screening with HPV DNA testing in older women) without modifying the underlying screening interval offer little incremental benefit while drastically increasing costs;
- Strategies, however, that employ more sensitive screening tests (e.g., liquid-based cytology with reflex HPV testing, cytologic assessment enhanced with computer-assisted imaging, and primary screening with HPV DNA testing in older women) in the context of screening every 3 to 4 years are extremely cost-effective;
- Small changes in specificity are very influential on cost-effectiveness in settings with frequent screening and aggressive follow-up strategies for women with abnormal screening test results;

- Strategies that capitalize on the information provided by HPV DNA testing (e.g., consecutive years of negative cytologic and HPV DNA testing results) and modify screening interval and strategy on the basis of this information, can be extremely cost-effective;
- For women in whom consecutive cervical cancer screening test results have consistently been negative, screening after the age of 65 years is not cost-effective. Conversely, for women who have had no prior screening, screening in older ages is very cost-effective.

3.4. Main themes from cost-effectiveness analyses of screening in settings without screening programs

- For countries with limited resources, screening efforts should target women age 35 or older, and strategies should focus on screening all women at least once in their lifetime before increasing the frequency of screening;
- If high coverage can be achieved, screening 2 to 3 times per lifetime could reduce lifetime cancer risk by 25% to 40%. Targeting the right age groups is crucial, generally around the age of 35 years; when screening 3 times in a lifetime, the tests should occur between the ages of 30 and 50 years, with a spacing of about 5 years;
- Choice should be made between HPV testing (most effective), visual screening methods (least costly), and cytology (most sensitive) relative to the need to screen and treat in fewer visits, required resources (amount and type), and sensitivity;
- Provided widespread coverage can be achieved, small changes in sensitivity have a greater impact on the population and are more cost-effective in settings providing infrequent screening; changes in specificity have a lesser impact on cost-effectiveness in the context of very infrequent screening;
- Key uncertainties for which better data are needed include the long-term effectiveness of cryosurgery in screen-and-treat strategies.

4. Projected impact and cost-effectiveness of HPV-16/18 vaccination

To adequately address policy questions involving vaccination and screening for a given country, and also take into account its particular resource requirements and operational challenges, different kinds of models are necessary.

4.1. Transmission models

A dynamic transmission model is required to assess the epidemiological changes in type-specific HPV prevalence over time; estimate the impact of herd immunity; explore the relative value of vaccinating girls alone vs. both girls and boys; and explore the impact of sexual mixing patterns on the projected HPV prevalence by age following vaccination [45—47]. Many parameters required for these models are unknown for HPV types other than HPV-16 [48]. Even for HPV-16, data are very limited for transmission rates in men and women, and detailed sexual behavior data stratified by variables such as sex, age, other risks, and health-seeking behavior are needed. Since there are so many unknowns, many simplifying assumptions are necessary. Transmission models that only include HPV-16, or that include both HPV-16 and HPV-18, cannot be used to project a comprehensive landscape of cervical cancer over time following vaccination because another 30% of cervical cancer cases (and a higher percentage in some regions of the world) are caused by other oncogenic types. And while the potential for cross-protection or cross-reactivity among HPV types seems plausible, they cannot be explored using a model designed for 1 or 2 types of HPV.

4.2. Disease simulation models

State transition models are well suited to represent simulation of chronic disease with multiple stages over a relatively long time (e.g., development of invasive cancer over 2 decades), as it can include considerable detail on different screening and treatment strategies, and accommodate the detailed cost and quality of life measures associated with each disease stage or health state [49]. Most published cervical cancer screening models are “closed” state transition models, in that no one enters or exits the cohort at any time during the simulation. State transition models can also be dynamic, in that they allow people to enter or exit the model over time. An advantage of closed models analyzed as cohort simulations is that they are transparent, they easily accommodate probabilistic uncertainty analysis, and they are rapid and efficient in terms of computing intensity. Variations of this basic model are necessary to stratify state of health according to HPV type; capitalize on time trends data for prevalence of age-specific HPV infection, risk factors, and invasive cervical cancer; and address more complex strategies that rely on the history of the individual woman to predict both her individual health risk and resource utilization, and tailor her subsequent screening strategy based

on that history. Two examples of work in this area include "open" population-based models, which allow for accommodation of trends over time, and first-order Monte Carlo simulation models, which allow the incorporation of many dimensions of heterogeneity (e.g., type of HPV and individual-based risk factors such as parity or smoking). These modeling options reflect both variability and uncertainty, and permit the risk of any event to depend on individual history [50].

Regardless of type all models can be simple or complex, and deterministic or probabilistic, but they all utilize a wide range of approaches to calibrate to data, estimate uncertain or unknown parameters, and evaluate uncertainty and variability. As a general rule, simplicity and complexity both involve tradeoffs. For example, including more detail means that more parameter values are required, and the model becomes more complicated and more difficult to analyze [49,51].

Although a detailed discussion of modeling methods is beyond the scope of this chapter, it is important to understand that no single type of model is perfectly suited to evaluate the cost-effectiveness of vaccination and screening. Increasingly, modelers are working together not only to help each other, but also to assist readers in understanding how these tools are used to assess the different components of policy problems more thoroughly.

There are several published analyses addressing the impact of HPV vaccines [46,52—59]. These model-based analyses differ in their objectives, and thus in their choice of model structure, although most intended to be exploratory, aiming to provide qualitative insight rather than directly inform decision making. The published models are briefly described below, with their main results summarized and the early themes of agreement identified.

4.3. Modeling the health impact of HPV vaccination

To explore the clinical impact of an HPV-16 vaccine, Garnett and Waddell [46] and Hughes, Garnett, and Koutsky [54] developed 2 dynamic transmission models based on (1) prevalence of HPV-16, and (2) incidence of cervical cancer. Beginning with 3 groups differing by level of sexual activity, the authors allowed the vaccine to reduce susceptibility of infection, reduce transmission of infection, or reduce duration of infectiousness. They found that sexual mixing patterns, rate of partner change, and the protective properties of the vaccine influenced the prevalence of HPV-16 infection. They found that when both men and women were vaccinated — assuming 90% coverage, 75% effectiveness, and 10-year immunity — type-specific HPV prevalence was reduced by 44%, but that when only women were vaccinated, it was reduced by 30%. The model also showed that if the vaccine only targeted certain types of high-risk HPV, cervical cancer incidence was not reduced by the same amount because infection with other high-risk types could progress to invasive cancer. The authors concluded by suggesting that a multivalent vaccine could be highly effective in reducing HPV infection and cervical cancer, yet underscored the need for continued cervical cancer screening efforts.

Goldie and colleagues [55] explored the impact of a type-specific HPV-16/18 vaccine using a cohort simulation model calibrated to population-based data for Costa Rica. They found that a vaccine that prevented 98% of persistent HPV-16/18 infection was associated with an approximately equivalent reduction in HPV-16/18-associated cancer and a 51% reduction in total cervical cancer. The effect on total cancer was attenuated because of the competing risks associated with oncogenic types of HPV other than HPV-16/18. Yet, even though the bivalent vaccine could be highly effective in reducing HPV infection and cervical cancer in countries that could afford the resources, screening would remain necessary. The impact of vaccination on cervical cancer incidence was explored under varying assumptions of effectiveness, coverage, waning immunity, cross-protection, and infection with high-risk oncologic types other than HPV-16 and HPV-18. One of the most important findings was the impact of the uncertainty about the natural history of high-risk infection in older women on the effect of different levels of waning immunity.

Barnabas and colleagues [52] developed a transmission model of HPV-16 infection and progression to cervical cancer and calibrated it to HPV-16 seroprevalence in Finland over time. The investigators capitalized on empiric sexual history and HPV seroprevalence data from a single population to estimate the transmission of HPV-16 between men and women, and explore the impacts of risk factors on observed changes in cervical cancer incidence over time. The model was used to estimate the transmission probability of the virus, look at the effect of changes in patterns of sexual behavior and smoking on age-specific trends in cancer incidence, and explore the impact of HPV-16 vaccination. At both low (10% in opportunistic immunization) and high (90% in a national immunization program) coverage of the adolescent population, vaccinating girls and boys had little benefit over vaccinating girls alone. The investigators estimated that vaccinating 90% of young women before they begin sexual activity had the potential to decrease by 91% the type-specific

cervical cancer incidence (e.g., the incidence of cancer associated with HPV-16). While Goldie and coworkers [55] found the same near-linear decrease in cancer cases associated with HPV-16 using the cohort simulation model calibrated to multiple HPV types in Costa Rica, they also reported the potential range of cervical cancers that might be observed with other carcinogenic HPV types.

5. Cost-effectiveness analyses of HPV vaccination

Most published cost-effectiveness analyses of vaccination have thus far been in settings with existing screening. Goldie and associates [56] explored the potential cost-effectiveness of vaccination in the context of current cervical cancer screening in the United States and evaluated vaccination at 12 years of age (under various assumptions of efficacy, waning immunity, and competing infection with HPV types other than HPV-16 and HPV-18) in combination with different Pap smear screening strategies that varied by starting age and frequency. Although the results were sensitive to various assumptions of duration of immunity, the authors concluded that a program of HPV-16/18 vaccination at the age of 12 years, coupled with triennial screening starting at the age of 25 years, decreased the lifetime risk of cervical cancer by 94% and was the most cost-effective strategy. Also, as a general rule, with more effective vaccines, less frequent cytologic screening produce equivalent protection against cancer. In a recent analysis integrating data on screening patterns by race in the United States, these investigators found that HPV-16/18 vaccination, while having very small incremental benefits at the population level in comparison to current screening, could reduce disparities substantially in terms of cervical cancer mortality if widespread vaccine coverage could be achieved. Qualitative results by other investigators were similar. Using an independent model, Kulasingam and Myers [57] found that a strategy of vaccination coupled with the postponement of screening to the age of 24 years was the most cost-effective strategy under base case assumptions of 75% effectiveness and 10-year immunity. Using assumptions similar to those of the other models regarding vaccination age (12 years), vaccine efficacy (75%), and duration of immunity (10 years), Sanders and Taira [58] found that vaccination was very attractive, costing $22,800 per QALY. Differences in results among these 4 models may be attributable to the assumptions of incidence of HPV infection, relative risks of cervical cancer based on HPV types, and estimates of cost.

Several cost-effectiveness analyses of vaccination in developing countries without existing screening are underway. Goldhaber-Fiebert and coworkers [60] and Ngwalle and coworkers [61] provide a brief description of preliminary results of an exploratory analysis conducted in Tanzania, where screening has not been feasible. The investigators calibrated a previously developed model of HPV and cervical cancer (1) to available data on cervical cancer incidence and mortality in Tanzania, and (2) to the percentages of precancerous lesions and invasive cancer caused by HPV-16 and HPV-18, other high-risk types, and low-risk types. They overlaid a simple vaccination model, allowing for incomplete population coverage, partial efficacy, and waning of efficacy. Lifetime costs, life expectancy, and cost-effectiveness ratios were estimated for vaccination alone, screening alone using HPV DNA testing or cervical cytology once in a lifetime at about 35 years of age, and vaccination plus screening.

In the most optimistic vaccination scenario evaluated (100% coverage, 90% effectiveness, and no waning of efficacy over time), the lifetime risk of cervical cancer was reduced by nearly 60% with HPV-16/18 vaccination in early adolescence; 12% to 43% by screening, depending on modality and frequency; and 66% to 80% by combining vaccination and screening. Cost-effective strategies included vaccination alone as well as vaccination plus screening once per lifetime, although the latter had greater benefits. Results were most sensitive to vaccination coverage, cost of administering the vaccine, and the duration of protection provided by vaccination.

It may be the case that establishing vaccination and screening programs simultaneously, even if found to be potentially cost-effective, would not be affordable given Tanzania's health care budget [62]. Therefore, it may be useful to consider a scenario where a decision maker was faced with a choice between vaccination or screening. Results from this exploratory analysis suggest that HPV vaccination in Tanzania may be promising and that a combined approach of vaccination of young girls and single lifetime screening of older women is likely to be cost-effective. HPV vaccination alone, under the base case assumptions, would have a cost-effectiveness ratio of 4% to 12% of the GDP, and HPV vaccination and a single lifetime screening around the age of 35 years would have a cost-effectiveness ratio of 50% to 73% of the GDP. Compared with other “good buys” in public health, these would all be considered cost-effective. This type of exploratory analysis can assist in subsequent clinical study design, evaluation of intermediate end points, and planning for operational delivery and sustainable strategies. It may also serve to motivate policymakers,

in-country stakeholders, ministries of health, international organizations, and funders to begin critical dialogue early. It cannot, however, given the uncertainties in the data, inform policy decisions.

6. Summary of findings from exploratory studies of vaccination

Different analyses reveal several common themes regarding the cost-effectiveness of HPV vaccination. All models agree that a type-specific HPV vaccine will reduce, but not eliminate, the risk of cervical cancer. In resource-rich settings, in the context of existing cervical cytology screening, a type-specific vaccine may significantly reduce the incidence of CIN 3 and cervical cancer associated with HPV-16 and HPV-18, although the potential magnitude of the clinical benefits will depend on the underlying effectiveness of the screening program. Moreover, the cost-effectiveness of vaccination will rely heavily on the willingness to initiate screening at a later age, to conduct screening less frequently, and to adopt a conservative approach to the follow-up of women with equivocal and mildly abnormal screening test results. All else being equal, it appears that vaccinating both men and women has a small incremental benefit over vaccinating women alone when coverage is high, and that vaccine benefit decreases as age at vaccination increases beyond the beginning of sexual activity. This body of published work has elucidated several data priorities, including a better understanding of the heterogeneity of vaccine response, of duration of immunity, and of the effects of type-specific vaccination on other HPV types. In resource-poor settings without existing screening programs, the clinical benefits of even a partially effective type-specific HPV vaccine are likely to be substantial compared with the status quo. The greatest benefits, within a framework that would still be cost-effective, would be with the vaccination of preadolescents, followed by 2 screenings per lifetime between the ages of 35 and 45 years. The cost-effectiveness of vaccination in developing countries, even if combined with 2 or 3 screenings per lifetime, will depend greatly on vaccine price, costs associated with achieving widespread population coverage, feasibility of delivering 3 doses of vaccine to a preadolescent population, and duration of vaccine-induced immunity.

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