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Cost-Effectiveness Analysis of a Quadrivalent Human Papilloma Virus Vaccine in Mexico

Luz Myriam Reynales-Shigematsu,[a] Eliane R. Rodrigues,[b] and Eduardo Lazcano-Ponce[a]

[a]*Instituto Nacional de Salud Pública, Cuernavaca, Morelos, Mexico*
[b]*Institute of Mathematics, Universidad Nacional Autonomous Mexico, Mexico, D.F., Mexico*

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Background and Aims. Cervical cancer is one of the main causes of death in women in low- and middle-income countries. Despite technological and scientific advances that allow an early detection of precancerous lesions and curative treatment of cervical cancer, Mexico and other Latin American countries have only been able to obtain a small decrease in the mortality rates for this kind of cancer. How to implement and sustain effective public health strategies for cervical cancer prevention, such as increasing cytology-based screening program coverage and implementing HPV-DNA testing and vaccination, are important questions. The aim of this study is to perform a cost-effectiveness analysis of the introduction of a quadrivalent (HPV 6/11/16/18) HPV vaccine into the public health system and evaluate the epidemiological and economic benefits on prevention of cervical cancer in Mexico.

Methods. A Markov model is used to simulate the natural history of HPV infection in a cohort of Mexican women to evaluate the cost-effectiveness of the cervical cancer screening strategy used in Mexico as well as the benefits of other potential strategies such as 1) vaccination only, 2) conventional cytology-based screening program only and 3) vaccination followed by screening. For the strategies that involve screening we have chosen screening intervals of 3 and 5 years. The model produces results that are reasonably close to the epidemiological data related to HPV and cervical cancer in Mexico.

Results. The quadrivalent HPV vaccine could reduce the probability of persistent HPV-16/18 infection by at least 60%, which would result in a near-proportional reduction in HPV-16/18-associated invasive cervical cancer and CIN 3.

Conclusions. The strategy of using only vaccination ($45 USD for three doses) as a preventive measure was a very cost-effective strategy in Mexico ($68USD/LYS). The strategy of vaccination with traditional screening of Pap test every 3 years produced higher cost by a lower performance of cervical cytology in Mexico, at a cost of $15,935 USD per life-year. The cost-effectiveness of the vaccination strategy was highly sensitive to age of vaccination, duration of vaccine efficacy, and cost of vaccination. The Mexican model predicts that a quadrivalent HPV vaccine will reduce the incidence of high- and low-risk-associated cervical cancer. A program of vaccination as a preventive strategy is likely cost effective. The results of this study could be of great value in decision-making for the implementation of an HPV vaccine as a public health policy in Mexico provided that the cost of each dose will be, at most, $15 dollars (USD) dollars, combined with HPV testing, the new strategy of national secondary prevention program.

Key Words: Cervical cancer, Screening program, Quadrivalent HPV vaccine (HPV 6/11/16/18), Cost-effectiveness analysis.

Introduction

Cervical cancer is one the main causes of death due to cancer in women in developing countries. Cervical cancer is a public health problem in developing countries with 470,606

Address reprint requests to: Eduardo Lazcano-Ponce, Instituto Nacional de Salud Pública, Av. Universidad 655, 1er. Piso, Col. Santa María Ahuacatitlán, 62508 Cuernavaca, Morelos, México; Phone: (+52) (777) 3293003; FAX: (+52) (777) 3111148; E-mail: elazcano@insp.mx

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incident cases and 233,372 deaths annually worldwide due to this malignant tumor (1). Eighty percent of these recorded events occurred in poorer countries where cervical cancer is the leading cause of malignant tumors among women. In Latin America and the Caribbean, during the year 2000, 77,291 incident cases and 30,570 deaths related to this cause were recorded (2). In Mexico, cervical cancer is the second most common malignant tumor among women of childbearing age and the main cause of death due to neoplasia among women >25 years of age in southern Mexico (3). Even though mortality rates for this type of cancer have decreased in the last 10 years, the mortality rate for cervical cancer reached a peak in 1989 and after this decreased significantly to 9.9 in 2006 (4). During the year 2000, the number of cytology tests conducted by the health sector reached 4,594,672 women. Given that, according to common Mexican practices, cytology tests must be performed every 3 years in order to increase the probability of a complete coverage of the target population (5). This number represents 57.8% of the program's target population for that year.

The causal role of HPV in all cancers of the uterine cervix has been firmly established biologically and epidemiologically (6). HPV DNA has been found in almost 90% of the cases of cervical cancer or its precursors. Current evidence indicates that >40% of cervical intraepithelial neoplasia (CIN 3) could progress to invasive cancer if not treated. More than 25% of the apparently normal ectocervix have presented type 16 HPV (7). Although HPV is a necessary cause of cervical cancer, it is not a sufficient cause. Thus, other cofactors are necessary for progression from cervical HPV infection to cancer. Long-term use of hormonal contraceptives, high parity, tobacco smoking, and co-infection with HIV have all been identified as established cofactors. Hernández Ávila et al. (7) conducted a study to assess the relationship between HPV16/18 types and cervical cancer in Mexican women. HPV16/18 types were tested in 148 new cases and 204 follow-up cases using the polymerase chain reaction technique (PCR). HPV16 was found in 48.3% of 60 new cases of cancer in situ, 48.8% of cases of invasive cancer, and in 13.2% of follow-up cases. HPV18 was found in only 6.7% of new cases of invasive cancer. Epidemiological studies conducted in Mexico show that the critical age for death caused by cervical cancer is during the reproductive years. Furthermore, those studies consistently identify reproductive risk factors associated with this pathology such as multiple childbirths with seven or more deliveries, a record of two or more sexual partners, 12 or more vaginal deliveries, debut of sexual activity <14 years of age, and age of first menstrual period >17 years of age (8).

Initial results with the HPV vaccines indicate that protection against persistent infection with HPV types 16 and 18 is ~100% in 5 years of follow-up (9–12). Ongoing phase-III studies are likely to corroborate these findings and show high vaccine efficacy against high-grade preneoplastic cervical lesions (13). This has motivated research to evaluate its potential public health benefit. Despite technological and scientific advances that allow early detection of precancerous lesions and curative treatment for cancer, Mexico has been able to obtain only a small decrease in the mortality rates related to this type of cancer (4). It has been found that some social, cultural, economic and institutional barriers obstruct this task (7). How to implement and sustain effective public health strategies for cervical cancer prevention, such as increasing cytology-based screening program coverage and implementing HPV DNA testing and vaccination, are important questions. However, no single empirical study can evaluate all possible strategies to report on these policy questions. By integrating the best biological, epidemiological, economic, and behavioral data, the use of modeling in an analytical decision framework can assist in early decision-making and can provide insight into the potential cost-effectiveness of different strategies (14).

The aims of this paper are to use the data from multiple cases of HPV and cervical cancer obtained from Mexican studies to perform a cost-effectiveness analysis of the quadrivalent HPV vaccine and its epidemiological impact in Mexico as well as to estimate the age-specific cervical cancer incidence, simulate the natural history of HPV infection, and evaluate the impact of the cytology-based screening strategy using the new impact with vaccine for screening comparison.

Patients and Methods

The Model

To achieve these objectives, a Markov model is used to simulate the natural history of HPV infection in a cohort of Mexican women beginning at the age of 12 and following them until the age of 85. This model is an adaptation of the one published in the study by Kulasingam and Myers (15). The main difference in this model is that HPV infection is separated into high- and low-risk types with different probabilities of progression. Specific parameters in the model were adjusted to provide a best-fit to the data available for Mexico. The parameters used in the model can be divided into four groups: demographic, epidemiological, economic, and those related to the vaccine. All data used in the model, with the exception of the progression and regression rates of the different stages of HPV infection, correspond to the female population in Mexico. The model takes into account all cervical intraepithelial neoplasia (CIN 1, 2 and 3) and invasive cervical cancer stages (stages I, II, III and IV) related to HPV infection of the high- (i.e., 16/18) and low-risk types (i.e., HPV 6/11).

Simulation Model Assumptions

Some baseline assumptions for the vaccine were considered. The effectiveness of the vaccination is limited to the

cohort itself, such that the results observed are due to the reduction of individual susceptibility to the infection rather than to the sexual transmission of HPV. The age of vaccination is 12 years and varied in sensitivity analysis between 12 and 25 years of age. It is assumed that the polyvalent vaccine to prevent infection by HPV is a quadrivalent vaccine, meaning that it immunizes against more than one type of virus. It is also assumed that the vaccine could be targeting 70% of all oncogenic types including HPV16/18 types (16,17) and 50% of all low-risk types (including HPV6 and HPV11) (18). The vaccine efficacy is assumed to be 95% according to publications in the literature and to vary in sensitivity analysis (12,13). A scheme of a sole vaccination with three doses that would protect an individual for their entire lifetime shall be assumed. This vaccine duration varied in sensitivity analysis between 10 and 30 years. Vaccine coverage is 100% and varied in sensitivity analysis. Because published data show that the vaccine has no or only slight minor side effects of minimal clinical importance, side effects were not considered in the simulation model (12,13).

Some baseline assumptions for the screening are also taken into consideration. The screening strategy starts at age 25 and ends at age 65. Screening coverage is assumed to be 30% for a conventional cytology-based screening program and varied in sensitivity analysis. Women who have an abnormal cytology test result are offered treatment and are assumed to receive colposcopy and biopsy. If both tests are positive, they are offered treatment according to the official Mexican guidelines for treatment of lesions related to cervical cancer (19). If they are negative, no treatment is offered.

Strategies Considered

In order to achieve the aims of this paper, several strategies were considered. Table 1 provides a list as well as a description of the preventive strategies considered in the present study. Strategy (2) corresponds to the one that is currently used in Mexico. Unfortunately, there is a high incidence of false negatives in cervical cytology laboratories in Mexico. Percentage of false negatives varies from 3.33−53.13% (3), producing a poor strategy of comparison between primary and secondary prevention.

Health Outcomes

Health units for measuring the population impact that we used in this study were cases of cancer and cancer deaths prevented. In order to compare the ratios across different studies, we estimate the life years saved (LYS), 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 (14).

Cost-estimation Assumptions

Given the large discrepancies between public and private costs, direct medical cost estimates were derived from the public health sector. We have been estimating health care costs related to the screening program, precancerous lesions (CIN 1, 2 and 3) treatment as well as stages of invasive cancer (stages I, II, III and IV) treatment using microcosting methods. We assumed that the vaccine would be applied within the current national vaccination program so that there would be no programmatic cost. Vaccine costs were based on hepatitis B vaccine price from different providers (private and public sector) and also from financial availability from the Ministry of Health in Mexico or public information data. All costs were estimated in Mexican pesos (MP, 2004) and discounted using the health sector component of the consumer price index from Banco de Mexico. For this study, costs were converted to U.S. dollars (USD) using the exchange rate (the amount of domestic currency required to purchase the same quantity of goods and services as $1 USD can purchase in the U.S.)

Table 1. Preventive strategies considered in the Mexican Markov Model

Strategies	Description	Notation used in Tables and Figures
(1) No intervention	No preventive measure is taken	NoPap
(2) Conventional Pap with coverage	The Pap test is applied to the cohort at the age of 25 and 26 according to the Pap coverage, from de the age of 27 on the cohort stays two years without receiving the pap tests and in the third year a Pap test is applied according to the Pap coverage	Pap3_Cov
(3) Vaccine only	The only preventive measure is vaccination and the vaccine is given to the entire cohort	Vacc
(4) Conventional Pap with coverage plus vaccine	The cohort is vaccinated according to the strategy (3) and a Pap test is applied according to the strategy (2)	Pap3_Cov + Vacc
(5) Conventional Pap with coverage every 5 years	A Pap test is applied according to a rule similar to that of strategy (2). The difference is that the time interval to which Pap test is applied is four years instead of two.	Pap5_Cov
(6) Conventional Pap with coverage every 5 years plus vaccine	The cohort is vaccinated according to the strategy (3) and a Pap test is applied according to the strategy (5)	Pap5_Cov + Vacc

(15,20,21). The exchange rate used is from December 2004, i.e., 1 USD=11.1 MP. Table 2 shows the direct medical costs.

Discounting

Discounting is the process of converting future costs to their present value, to reflect the fact that, in general, individual and society have a positive rate of time preference for consumption now over consumption in the future. 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 (22,23). For this study we used a 3% discount rate, a cost of $1 USD next year would be equivalent to $0.97 U.S. today. A discount rate of 6% is also explored using sensitivity analysis (22,23).

Program Cost and Cost of Scaling-up Intervention

Program costs are defined as those incurred at the administrative level outside the point of delivery of health care benefits, that means 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 costs of achieving incremental increases in coverage rates (22,23). There are no empirical data on any of these for a three-dose vaccine targeting adolescents. An additional important question that is facing many governments is the cost of scaling-up interventions to achieve target coverage levels, which means 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. For this reason, WHO-CHOICE recommended the cost-effectiveness analysis at coverage levels of 50%, 80% and 95% (22,23).

Cost-effectiveness Analysis (CEA) Assumptions

The central purpose of CEA is to compare the relative value of different interventions in creating better health and/or longer life. The results of such evaluations are summarized in a cost-effectiveness ratio where the denominator reflects the gain in health from an intervention and the numerator reflects the cost of obtaining that health gain. Comparative performance of alternative screening strategies is measured by the incremental cost-effectiveness ratio (ICER), defined as the additional cost of a specific screening strategy divided by its additional clinical benefit, compared to the next least expensive strategy (22,23). This ratio is a measure of value for resources, representing the average, additional resource consumption required to extend life expectancy in the population by 1 year. Thus, in this ratio, changes in resource use (relative to the stated alternative strategy) are captured in the numerator and valued in monetary terms, and health effects of a strategy (relative to a stated alternative strategy) are captured in the denominator. When one strategy is both more effective and less costly (in terms of life expectancy) than an adjacent strategy, it is said to dominate the alternative. Strategies that have higher ICERs than adjacent strategies are also said to be dominated (22,23).

Table 2. Screening test, premalignant lesions and cervical cancer diagnosis and treatment unitary cost (Mexico model)

	Direct medical care cost (USD)
Screening test	
Conventional PAP	$25
Diagnostic and treatment cost of premalignant lesions	
Colposcopy	$43
Biopsy	$18
Colposcopy and biopsy	$61
Cold knife conization	$96
Simple hysterectomy	$778
CIN 1	$48
CIN 2	$69
CIN 3	$1,382
Diagnostic and treatment cost of cervical cancer according to cancer stage at diagnosis	
Radical hysterectomy	$1,092
Laparotomy	$944
Pelvic exenteration	$1,100
Hospital day care	$368
Stage I	$6,702
Stage II	$8,641
Stage III	$6,067
Stage IV	$7,415
HPV vaccine	
Vaccine (3 doses)[a]	$57
Vaccine (3 doses)[b]	$236
Vaccine (3 doses)[c]	$45

All cost are converted from Mexican Pesos (MP) to USD according to the December 2004 exchange rate (1 USD=11.1 MP).
[a]Hepatitis B vaccine cost (CDC cost).
[b]Hepatitis B vaccine cost (private sector cost).
[c]HPV vaccine cost (better estimation for public sector cost).

Results

Model Calibration

Available data on age-specific HPV incidence was used to generate HPV incidence parameters for the model, compare the model-generated age-specific HPV prevalence to observed data, and adjust the incidence (within observed confidence limits) to approximate HPV prevalence. Because we modeled a cohort from cross-sectional data, we placed an emphasis on calibration data in younger women. That is mainly because there are differences in prevalence in older women (age-specific HPV prevalence among women of the >60 age group shows a second peak) that may well represent one or more nonmutually exclusive mechanisms that we are unable to model. The reasons for

the second peak and its geographic variation are unclear but may be influenced by reactivation of previously undetectable infections acquired earlier in life, may occur due to gradual loss of type-specific immunity, hormonal influences during postmenopausal years and another plausible reason is a cohort effect (24). Available age-specific mortality data for Mexican women was used as the primary competing risk after subtracting age-specific mortality rates for cervical cancer. In many countries, hysterectomy for causes other than cancer is also a leading competing risk affecting cervical cancer incidence. However, sufficient data were not available for Mexico to allow incorporation of hysterectomy into the model. An excellent fit of cervical cancer mortality rate produced by the model is shown in the Figure 1.

HPV Vaccine Impact on High- and Low-risk HPV Prevalence

Figure 2a shows the results produced by the model about the impact on the high-risk prevalence resulting from the different preventive strategies. HPV vaccine strategies decreased high-risk HPV peak prevalence from 20% to 7% (21 years). Figure 2b shows the impact on low-risk HPV prevalence. Strategies related to HPV vaccine decreased low-risk HPV peak prevalence from 3.6% to 2.3% (23 years). HPV vaccine is more effective in women <25 years old.

Cervical Cancer Incidence and Mortality

Figure 3 shows the impact on the incidence of cervical cancer resulting from different preventive strategies considered here and described earlier. When compared to the NoPap strategy, HPV vaccine strategies decreased the peak cancer incidence from almost 130 cases/100,000 to <40 cases/100,000.

Table 3 presents the cumulative number of cervical cancer cases avoided according to different strategies. Compared with the reference strata (NoPap), the vaccine alone could reduce cervical cancer cases by ~70%. However, the addition of a Pap smear strategy within an adequate interval could reduce cases by $>75\%$. Table 3 also presents the cumulative number of cervical cancer deaths prevented according to different strategies. Compared with the reference strata (NoPap) where the number of deaths was 3714, the vaccine alone could prevent >2600 deaths due to cervical cancer. Nevertheless, the addition of the Pap smear strategy in a 3-year interval could prevent almost 2900 deaths.

Cost-effectiveness Analysis

Figure 4 shows the cost-effectiveness results displayed on an efficiency curve where the discounted lifetime cost (horizontal axis) and discounted life expectancy (left vertical axis) of different strategies performed are shown. Strategies lying on the efficiency curve dominate those lying to the right of the curve because they are less costly and more effective or have a more attractive cost-effectiveness ratio than the next best strategy. As shown, the strategies that require a Pap smear only every 3 or 5 years are dominated or the least desirable strategies because they are more costly and less effective. The vaccine-alone strategy in a lifetime is the least costly and most effective dominate strategy at $68 USD/LYS. In fact, one of the less effective and most costly strategies was the conventional cytology test, which has been the recommendation for the last 20 years in Mexico and other developing countries. The

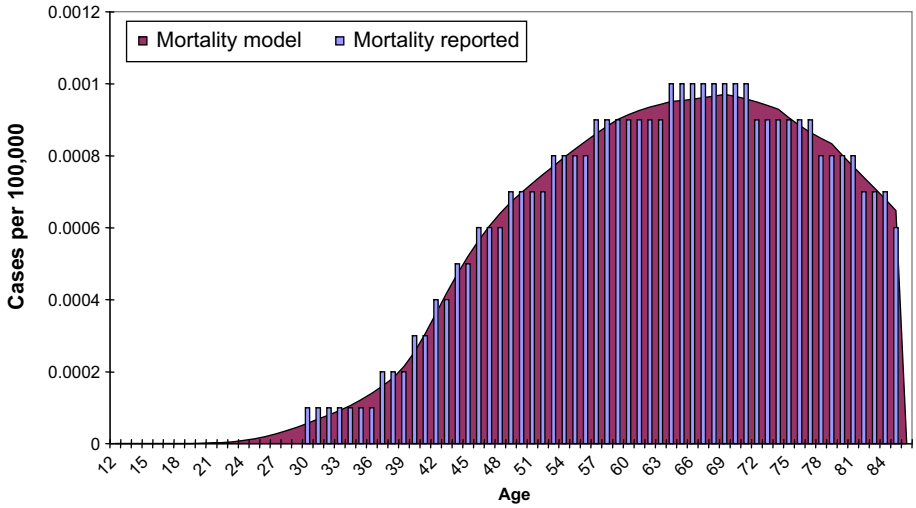

Figure 1. Age-specific cervical cancer incidence and mortality rate modeled. Mexico model. Color version of this figure is available online at www.arcmedres.com.

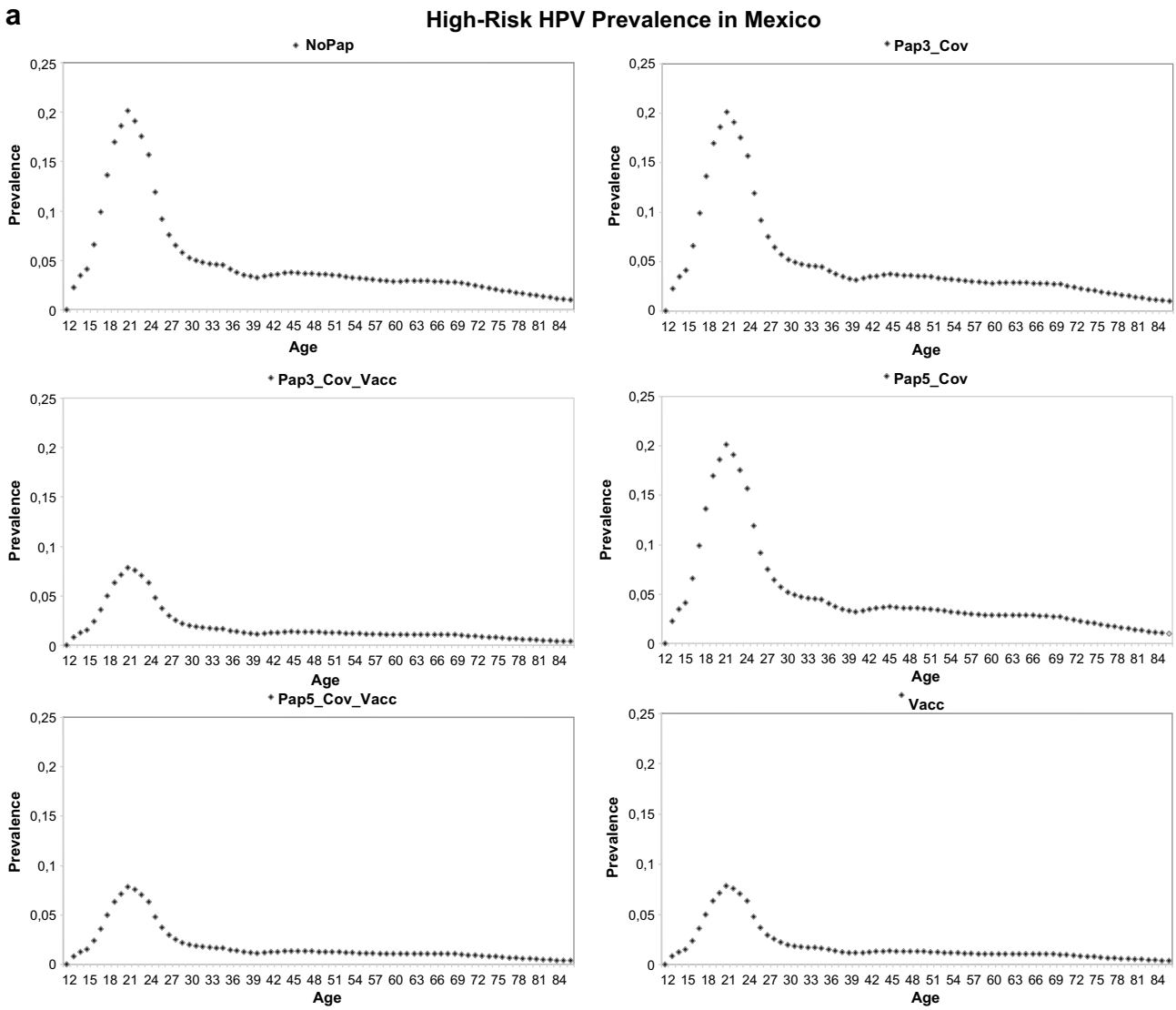

Figure 2. HPV prevalence according to the preventive strategy in Mexico. (a) High-risk type. (b) Low-risk type.

strategy of vaccination with screening every 3 years had the largest overall reduction (>75%) in cancer incidence and mortality at a cost of $15,935 USD per life year saved compared with screening every 5 years. The Commission on Macroeconomics and Health recently defined interventions that have a cost-effectiveness ratio less than the GDP per capita as very cost effective. Using Mexico-specific GDP per capita ($6,178 USD) (25) as a threshold, vaccination alone would be considered a very cost-effective strategy (26). Because of the interaction between cost-effectiveness, disease burden, and available funds, the cost effectiveness ratio alone is not the only factor to priority setting; additional criteria such as affordability, distributional impacts and equity considerations, capacity to deliver interventions, and public preferences should be addressed (14).

Sensitivity Analysis

We focused our sensitivity analysis on the vaccine and cytological screening coverage as well as interval variables to identify the largest cost-effective strategy for Mexico. Univariate analysis indicated that the cost of the vaccine at $45 USD is considered a very cost-effective strategy (Figure 5). The minimum vaccine coverage to assure a cost-effective ratio is 30%. The cost-effectiveness of vaccination was highly sensitive to age of vaccination, duration of vaccine efficacy and cost of vaccination.

Discussion

Given that the most relevant public health and policy questions related to cervical cancer control differ in developed

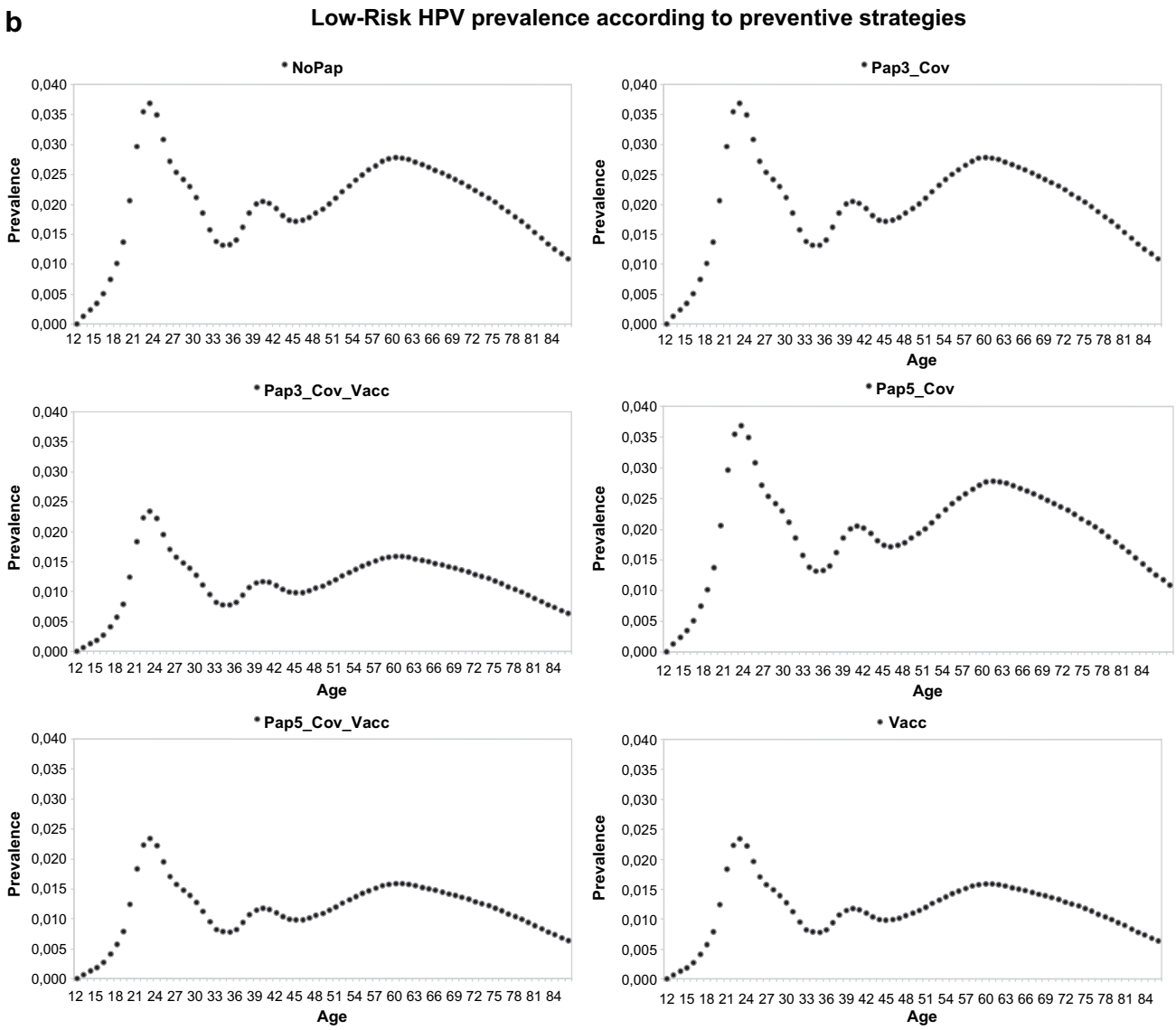

Figure 2. Continued

and developing countries and the prospect that an effective HPV vaccine is actually commercially available, we have conducted an effectiveness analysis for adding vaccination to an existing screening program. This cost-effectiveness analysis was made using Mexican data as an approach of Latin American countries where HPV infections are endemic (27) and with high incidence and death rates from cervical cancer (28). Using a Markov model, we have combined epidemiological, clinical and economic data from multiple studies conducted in Mexican women and published by several authors over the last 15 years. The model used here simulates the natural history of the infection by HPV in a cohort of Mexican woman beginning at the age of 12 and following them until the age of 85 years. The model also evaluates a potential vaccine which targets 70% of all oncogenic types and 50% of all low-risk types. Our findings suggest that a vaccine with an efficacy of 95% (12) can reduce about 10% of high-risk and 2% of low-risk HPV prevalence, respectively, during peak infection incidence (i.e., for women <25 years old). It is important to mention that the key to overall vaccine effectiveness depends on adequate protection during the ages of peak HPV oncogenic incidence, age of vaccination, HPV types covered, vaccine efficacy and duration of efficacy (12). The model was calibrated to achieve the best possible fit to population-based data and validated by predicting outcomes (cervical cancer incidence and mortality, age-specific CIN 1, 2 and 3 prevalence) consistent with observations of populations of Mexican woman. The model predicts that 100% of vaccine coverage could be successful in reducing the incidence of cervical cancer by 70% and, if a cytology-based screening program were also well

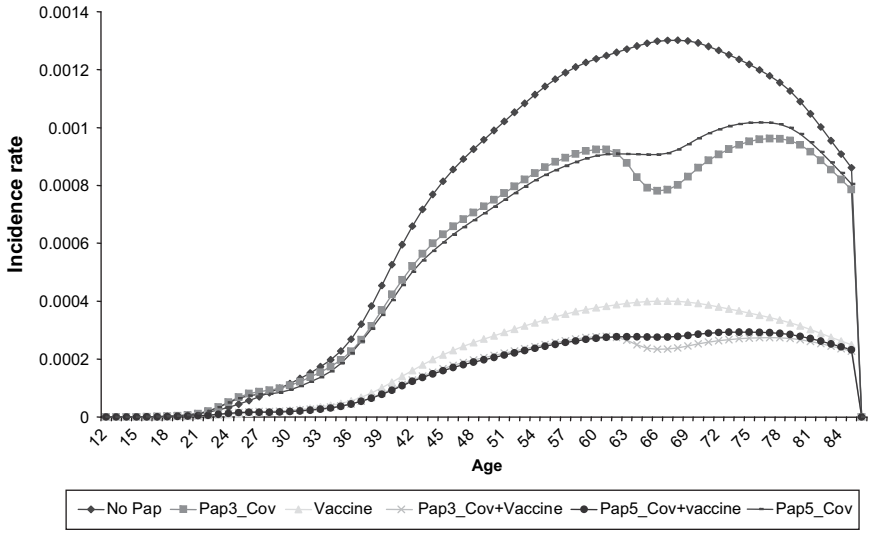

Figure 3. Cancer incidence according to the preventive strategy in Mexico.

implemented, the incidence could be reduced by 75%. Even though the purpose of this study was to conduct a comparative analysis of clinical benefits of alternative cervical cancer screening strategies in Mexico, a new diagnosis test for early detection for pre-malignant lesions such as a HPV DNA test, was not considered as an alternative for comparison to primary prevention. We have modeled the conventional cytology test considering the current screening standards and determining different cytology test intervals that could be effective in Mexico. Our results validate the assumption that an HPV vaccine added to a proper screening program would achieve a significant reduction in the incidence and mortality rates of cervical cancer (29). Therefore, those combined strategies may be the best strategy for preventing and controlling cervical cancer epidemics in developing countries like Mexico, even though they are not cost-effective, particularly for the very poor performance of the Pap test in Mexico (30). In view of the strong evidence base concerning cervical cancer prevention technologies in the region and the expected impact of vaccination on the performance of cytology, we propose a reformulation of cervical cancer screening policies to be based on HPV testing using validated methods followed by cytologic triage. This approach would serve as the central component of a system that plays the dual role of providing screening and surveillance as integrated and complementary activities, sharing centralized resources and coordination.

The model presents some limitations such as a significant uncertainty about many of the parameter estimates both in terms of progression and regressions probabilities, ranging from age-specific mortality rates from causes other than cervical cancer to the duration of vaccine efficacy. When choosing parameter values, we have erred on the side of conservatism—using cost and probability estimates that underestimate the likely effectiveness and cost-effectiveness of a vaccine. The model simulates an imaginary cohort. Although this is useful for modeling vaccine impact, it does not take into account the impact on women at other ages in terms of screening. Simulating the effectiveness of strategies in a population with varying age distributions would affect results although this approach is problematic as well (31). The model does not take into account the potential benefits and cost-savings of a nonmalignant 6/11 HPV component. Because there are no data available on the incidence of genital warts in Mexican women, and thus no data on the costs associated with treatment of genital warts, we cannot provide any estimate of this impact. An exploratory analysis in the U.S. suggests that adding a 6/11 component results in substantial cost savings (as well as improvement in quality of life). Unless a vaccine active against 6/11 in addition to 16/18 is considerably more expensive than one active against 16/18 alone, or unless the costs to the health system associated with

Table 3. Cumulative avoided cervical cancer cases and deaths according to different preventive strategies (Mexico model)

	Cervical cancer cases		Cervical cancer deaths	
Strategy	Cumulative avoided cases/100,00	%	Cumulative avoided deaths/100,000	%
No. Pap[a]	5,265	–	3,714	–
Pap3_Cov	1,026	19.50	898	24.18
Vaccine	3,748	71.20	2,646	71.25
Pap3_Cov + Vaccine	4,068	77.27	2,921	78.64
Pap5_Cov + Vaccine	3,970	75.41	2,839	76.43
Pap5_Cov	710	13.49	628	16.91

[a]Reference strata.

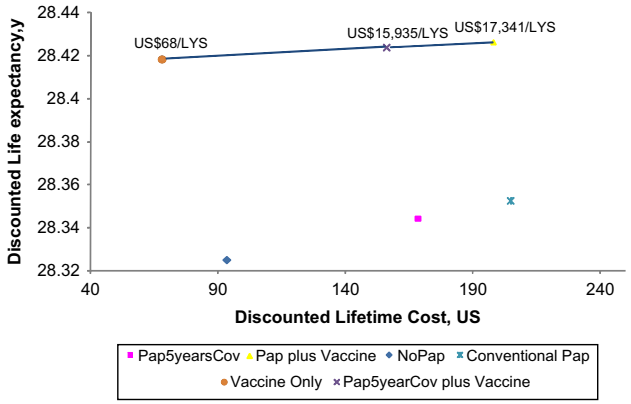

Figure 4. Efficiency curve comparing different cervical cancer strategies in Mexico. Color version of this figure is available online at www.arcmedres.com.

6/11 disease are negligible, a quadrivalent vaccine will be more cost-efficient than a bivalent vaccine for a high-risk population for clinical lesions.

The model does not take into account the effects on reduction in transmission or the possible additional effectiveness of vaccinating men. However, an important observation from comparing the results from different modeling exercises (cohort vs. transmission dynamics models) is the similarity of the results (32) including Mexican estimation (33). Barnabas et al. (34) estimated that vaccinating 90% of young women before sexual debut has the potential to decrease HPV type 16-specific cervical cancer incidence by 91%. Goldie et al. found this same near linear decrease in type-16-associated cancer alone, using the cohort simulation model calibrated to Costa Rica. This suggests that for many scenarios, state-transition models analyzed using cohort or Monte Carlo simulation provide an adequate representation of vaccine impact on cervical cancer (35).

During 2003, Mexico spent 6% of its total health care expenditures on the reproductive health program; 8% of this expenditure ($176 million USD) was allocated to the cervical cancer program (36). The Ministry of Health (SSA) invested an enormous budget to strengthen efforts oriented to improve the poor quality of the Pap smear diagnosis, connoting a decrease in the high rate of false negatives. Therefore, the most important result of this model is to propose a prophylactic HPV vaccine as a highly effective strategy that has a marginal cost when compared to the required investment to implement a better screening program based on Pap smears. This cost differential already exists without considering the costs that would be required to improve the cervical cytology. By implementing HPV vaccination, the age of the first cervical cytology test can be delayed to later age in life with less periodic screenings. This translates to a more cost-effective use of the available health resources (18) while guaranteeing a good standard of care. It is known from previous mathematical simulation models that more sensitive diagnostic tests for cervical cancer and/or the increased frequency in screening dramatically increase the costs and simultaneously diminish the quality of such indicators (37). For this reason, while introducing a primary prevention strategy like HPV vaccine to the population of a developing country, the search for more sensitive diagnostics alternatives should still continue. Women who are most often screened are those who least need it—the urban rich. The rural poor with the least access to screening are at highest risk for cervical cancer. Despite years of effort in many countries, this imbalance has not been adequately addressed. Immunization with the HPV vaccine offers a new method to address this problem.

The HPV vaccine alone could reduce the probability of persistent HPV16/18 infection by at least 60%, resulting in a near-proportional reduction in HPV16/18-associated invasive cervical cancer and HSIL. This model is a precedent for Latin American countries that share similar organizational deficiencies in cervical cancer screening programs. The decision of introducing a prophylactic HPV vaccine as a public health policy in developing countries should be based on four relevant points: 1) Knowledge of disease burden in the reference areas. In Mexico, during the last 25 years $>$85,000 deaths were attributed to cervical neoplasia. Each year about 30,000 new cases are detected and, over the last 30 years, cervical cancer has been considered one of the most frequent causes of death for women, after breast cancer. 2) Another point that should be considered is the frequency data for HPV in the population. Previous reports have asserted that the vaccine should be offered universally and not be focused solely on populations with high-risk sexual activity. The reason for that is that HPV would circulate at a high rate in several geographic areas (6) before the HPV vaccine could be effective as a primary intervention. Mexico can already be considered an endemic region for HPV infection. HPV frequency is elevated among women in the population, with a prevalence of 12% (38). The prevalence is also high among men, where in high-risk sexual activity groups the presence of HPV DNA can be found in 1/2 or 3 Mexican men (39), which translates to a prevalence in external genitals as high as 46%. 3) The third element to consider for introducing a cervical cancer screening program is health services facilities. Developing countries have many priorities; therefore, the introduction of an HPV vaccine should be cost-effective. Hence, introducing a vaccination strategy would not imply adding costs to the cost of the vaccine. 4) Mexico has a regulatory agency that oversees the introduction of new therapeutic agents called the Federal Commission for the Protection against Sanitary Risks (COFEPRIS). It is an agency similar to the U.S. FDA and their purpose is to evaluate the safety and efficacy of new drugs.

Three additional elements should be considered: (a) guarding of patient rights and maintenance of medical ethics. In Mexico, for patients $<$18 years of age, parental

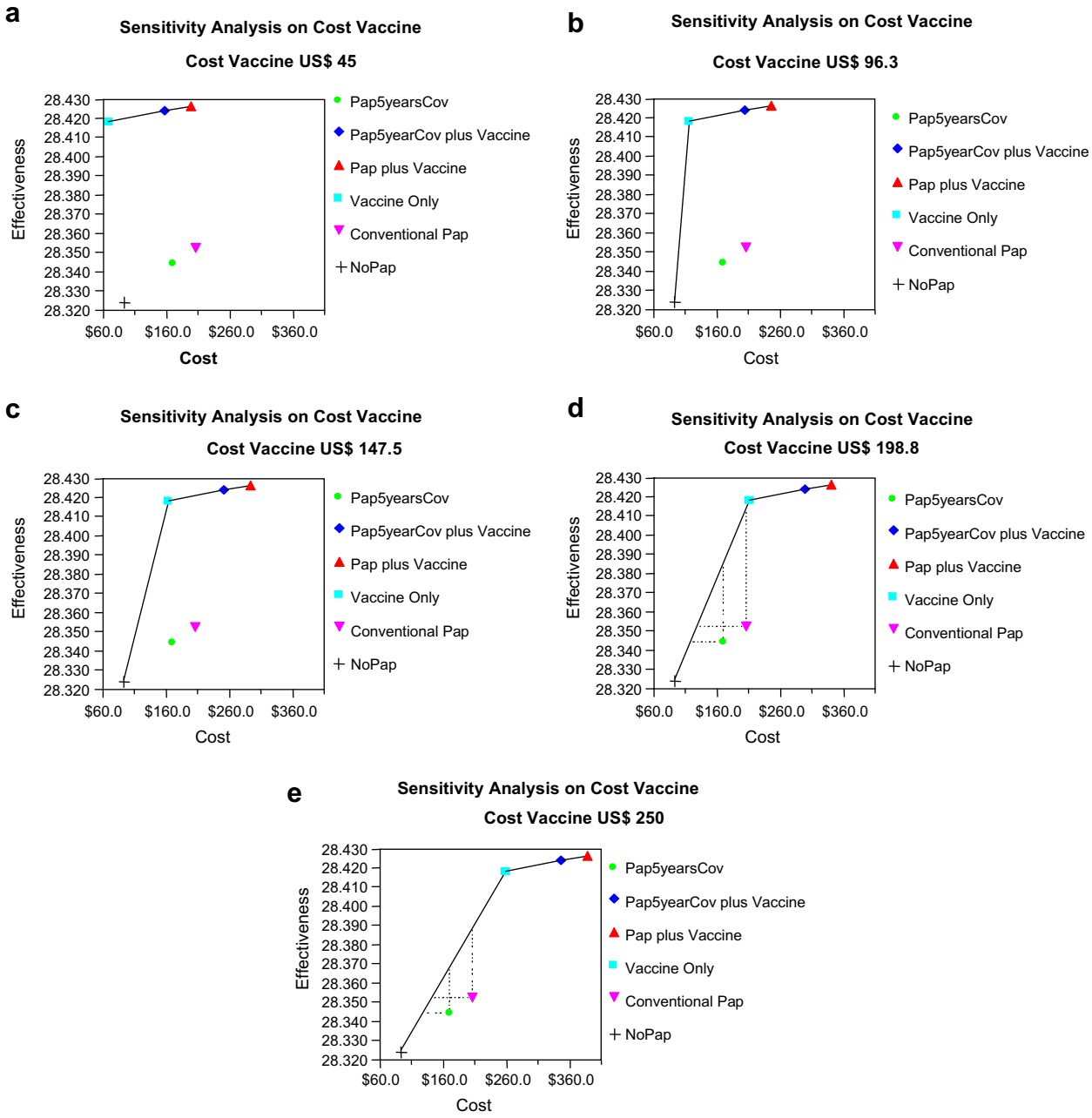

Figure 5. Sensitivity analysis, HPV vaccine cost. Color version of this figure is available online at www.arcmedres.com.

consent would be required to administer a vaccine that protects against sexually transmitted diseases. (b) The coverage of the vaccination in developing countries depends on available funds and the price of the vaccine and, finally, (c) it is necessary to promote the acceptability and knowledge of the vaccine among the different ''players,'' including decision- and policy-makers, health-care personnel, teachers, parents, and adolescents. For policy-makers considering the introduction of a primary prevention intervention for the general public, in addition to the information presented in this paper, the feasibility, sustainability and the accessibility of the program by the population at risk should be considered (40).

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