

## A COMPREHENSIVE NATURAL HISTORY MODEL OF HPV INFECTION AND CERVICAL CANCER TO ESTIMATE THE CLINICAL IMPACT OF A PROPHYLACTIC HPV-16/18 VACCINE

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The object of our study is to project the impact of a prophylactic vaccine against persistent human papillomavirus (HPV)-16/18 infection on age-specific incidence of invasive cervical cancer. We developed a computer-based mathematical model of the natural history of cervical carcinogenesis to incorporate the underlying type-specific HPV distribution within precancerous lesions and invasive cancer. After defining plausible ranges for each parameter based on a comprehensive literature review, the model was calibrated to the best available population-based data. We projected the age-specific reduction in cervical cancer that would occur with a vaccine that reduced the probability of acquiring persistent infection with HPV 16/18, and explored the impact of alternative assumptions about vaccine efficacy and coverage, waning immunity and competing risks associated with non-16/18 HPV types in vaccinated women. The model predicted a peak age-specific cancer incidence of 90 per 100,000 in the 6th decade, a lifetime cancer risk of 3.7% and a reproducible representation of type-specific HPV within low and high-grade cervical precancerous lesions and cervical cancer. A vaccine that prevented 98% of persistent HPV 16/18 was associated with an approximate equivalent reduction in 16/18-associated cancer and a 51% reduction in total cervical cancer; the effect on total cancer was attenuated due to the competing risks associated with other oncogenic non-16/18 types. A vaccine that prevented 75% of persistent HPV 16/18 was associated with a 70% to 83% reduction in HPV-16/18 cancer cases. Similar effects were observed with high-grade squamous intraepithelial lesions (HSIL) although the impact of vaccination on the overall prevalence of HPV and low-grade squamous intraepithelial lesions (LSIL) was minimal. In conclusion, a prophylactic vaccine that prevents persistent HPV-16/18 infection can be expected to significantly reduce HPV-16/18-associated LSIL, HSIL and cervical cancer. The impact on overall prevalence of HPV or LSIL, however, may be minimal. Based on the relative importance of different parameters in the model, several priorities for future research were identified. These include a better understanding of the heterogeneity of vaccine response, the effect of type-specific vaccination on other HPV types and the degree to which vaccination effect persists over time.

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**Key words:** HPV; cervical cancer precursors; invasive cervical cancer; vaccine; modeling

In the past several years there have been substantial advances in our understanding of the epidemiology of cervical carcinogenesis and the causal role of oncogenic human papillomavirus (HPV).<sup>1–3</sup> Despite this scientific progress, cervical cancer continues to have a devastating impact on women worldwide, with an estimated 400,000 women developing cervical cancer and 200,000 dying from this disease each year.<sup>4–7</sup> From the perspective of developing countries, where less than 5% of women are ever screened, the development of a preventive vaccine may offer the most feasible option to reduce cervical cancer mortality.<sup>8,9</sup>

A growing body of evidence implicates persistent HPV infections, particularly with oncogenic types, in the cause of squamous

intraepithelial lesions (SIL) and cancer.<sup>10–13</sup> Persistent HPV infection results in inactivation (by the E6 and E7 proteins of the HPV genome) of p53 and pRb tumor suppression genes, leading in turn to increasingly severe intraepithelial neoplasia and eventually to cancer. HPV DNA has been detected in up to 99.7% of all cervical cancers, and infection with 2 types (HPV-16 and HPV-18) accounts for more than 50% of all cervical cancer diagnosed each year.<sup>14,15</sup> A prophylactic vaccine that reduces or prevents high-risk infections such as HPV-16 and HPV-18 is likely to also prevent the development of HPV-16 and HPV-18 induced cervical cancer.<sup>9,16,17</sup> Recent results from a Phase II trial of an HPV vaccine showed 100% efficacy over 18 months in preventing persistent HPV-16 or HPV-16-specific cervical intraepithelial neoplasia (CIN), and Phase III trials of vaccines targeted against different oncogenic HPV types are underway.<sup>18</sup>

A number of factors must be explicitly considered in order to accurately evaluate and quantify the public health benefits of a potentially effective vaccine: accurate specification of the underlying natural history of disease; an understanding of the heterogeneity of risk in the target population; information with respect to competing morbidity and mortality in the global region of interest; and finally, vaccine program accessibility, compliance and feasibility. No clinical trial or single longitudinal cohort study will be able to consider all of these components and assess all possible strategies in all populations. A decision analytic approach using a mathematical simulation model can be a useful tool with which to evaluate alternative strategies by extending the knowledge from empirical studies to real-world situations.<sup>19–21</sup> For example, in the context of settings in which cervical cancer screening occurs, what would we expect in terms of observed prevalence of HPV, low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL) if the population were vaccinated? This information will be crucial for planning health policy initiatives that involve both screening and vaccination, and forecasting the likely health economic consequences associated with different programs.

Decision analytic models can also assist in the design of future clinical trials.<sup>22</sup> For example, CIN 3 has historically been consid-

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ered the strongest surrogate for cervical cancer; however, the totality of evidence supporting the role of persistent HPV infection in development of cervical cancer suggests that using “persistent infection” as a surrogate marker in clinical studies may also be reasonable.<sup>23</sup> Mathematical modeling techniques using the best available epidemiologic data can provide insight into the implications of using persistent HPV infection vs. CIN 3 as a surrogate marker in future vaccine trials.

Motivated by the challenges outlined above, our objective was to explore the clinical and public health implications of a type-specific HPV vaccine. We developed a computer-based model capable of simulating the entire spectrum of cervical disease stratified by HPV types which was built upon the foundation of previous cervical cancer models.<sup>24–34</sup> We used the model to project the impact of a prophylactic vaccine against persistent HPV 16/18 infection on the burden of disease attributable to cervical cancer, and to explore the potential effect of vaccination on the overall prevalence of HPV, LSIL and HSIL.

## MATERIAL AND METHODS

### *Analytic overview*

We developed a model capable of simulating the natural history of HPV infection and cervical carcinogenesis while incorporating the underlying type-specific HPV distribution within each stage of cervical disease. The model was used to assess the impact of a prophylactic HPV-16/18 vaccine on the age-specific incidence and lifetime risk of invasive cervical cancer, precursor cervical lesions and type-specific infection with HPV. The natural history of disease was modeled as a sequence of transitions among mutually exclusive health states. These states were defined using: 5 general categories of HPV infection (persistent HPV 16/18, persistent non-16/18 high-risk HPV types, persistent low-risk HPV types, transient low or high-risk types of HPV and no HPV); 3 categories of cervical disease (no neoplasia, cervical intraepithelial neoplasia 1 (CIN 1), cervical intraepithelial neoplasia 2,3 [CIN 2,3]); and 4 categories of invasive cervical cancer based on the staging system of the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) system (Stage I, Stage II, Stage III and Stage IV).<sup>35</sup>

Studies that have examined the risk of cervical neoplasia associated with persistent HPV have defined “persistence” in a variety of ways.<sup>10–12,36–45</sup> We stratified the HPV sector of health states into categories that were consistent with the classification used in the main clinical studies from which the parameter estimates for the incidence of HPV were derived.<sup>10,46,47</sup> The HPV stratum reflecting persistent high-risk types of HPV was further stratified into 2 groups: one to represent persistent infection with HPV types 16 or 18; one to represent persistent infection with HPV non-16 or 18 high risk types (e.g., 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68). The HPV stratum reflecting persistent low-risk types included women with all other HPV types.

For the purpose of this analysis, the model is described using the Bethesda classification nomenclature because the majority of recent studies that include data on HPV report their results using this system.<sup>48,49</sup> Health states referred to as LSIL in the natural history model represent CIN 1, and those referred to as HSIL represent CIN 2,3 and CIS (carcinoma *in situ*). Since the variable risk of progression to invasive cancer can be difficult to adequately capture using a single health state to represent CIN 2,3 and CIS, we stratified HSIL into 2 health states to reflect its heterogeneous natural history.

The time horizon of the analysis incorporated a woman's entire lifetime and was divided equally into 6-month increments, referred to as Markov cycles, during which women “transitioned” from one health state to another. Transitions between health states occurred once within each Markov cycle and were dictated by transition probabilities that were time-dependent. We chose a cycle length of less than 1 year to permit a realistic simulation of the natural history of HPV infection.<sup>10,12,38,50–52</sup> A cohort of 100,000 13-year-

old adolescent girls entered the model and faced age-dependent probabilities of acquiring HPV infection. Individuals simultaneously moved through the model according to transition probabilities based on their current cytologic and infection status. In the natural history model, all cases of cervical cancer were assumed to require persistent infection with HPV, reflecting the consensus that HPV infection is the causative agent for the vast majority of cervical cancers.<sup>1,14,15</sup> This may appear to conflict with epidemiologic studies in which a proportion of cervical cancers “appear” to occur in the absence of persistent HPV infection.<sup>14,15,53</sup> However, the best available data support that the vast majority of cancers without prior “detectable HPV” are observed as such due to limitations in the sensitivity of HPV DNA assays and the periodic nature of screening within studies.<sup>54,55</sup>

We assumed that acquired HPV infection could be persistent or transient. Women with either transient or persistent HPV infection could “clear” their HPV, although the probabilities governing infection clearance were specific to the type of HPV infection. Women who acquired HPV infection could develop histopathologic cervical changes, and those with CIN 1 and with CIN 2,3 could progress, regress or stay the same. The probabilities governing each of these transitions were conditional on the type of HPV infection; for example, women with persistent high-risk types of HPV were at greater risk of developing CIN 2,3 than those with persistent low-risk types of HPV. Women who experienced a single transient HPV infection did not develop CIN 2,3 or invasive cancer. In each cycle women with invasive cancer could develop symptoms or progress to the next stage of cancer. We assumed symptomatic women with invasive cancer received stage-specific treatment for their disease and were subject to the corresponding stage-specific survival rates. From every health state and in every cycle, women faced competing all-cause mortality risks.<sup>56</sup>

### *Modeling the impact of vaccination*

We assumed that: (i) an effective vaccine would reduce the probability of acquiring persistent infection with HPV 16/18 by 50%, 75% and 98%; (ii) 100% of the adolescent cohort is successfully vaccinated prior to their first exposure to HPV; (iii) adolescents receive 3 doses of the vaccine and are fully immunized by age 13 when the simulation begins; (iv) recipients of an effective vaccine are subject to the competing risks associated with acquisition of other HPV types; (v) vaccination has no impact on HPV-16/18 infections that are destined to be transient; (vi) vaccine efficacy does not wane over time. Because of the uncertainty as to the real-world performance of a prophylactic vaccine against HPV 16/18, we explored alternative assumptions about vaccine efficacy, waning immunity, infection with non-16/18 oncogenic HPV types in women vaccinated against HPV 16/18 and vaccination coverage rates.

### *Clinical data*

A comprehensive review of the published literature was conducted to define plausible ranges for the model parameter values (Table I).<sup>10–12,37,45,50–52,57–73</sup> Bibliographic searching was supplemented by secondary manual searches of recent publications not yet indexed into online databases, manual searches of several journals, online searches of Web sites specific to cervical cancer and consultation with an expert panel. Transition probabilities required by the model that were not available from primary data were imputed using calibration exercises conducted in 3 sequential steps: (i) the face validity of the model was assessed by projecting a series of intermediate and long term outcomes for which there were suitable existing data in the absence of screening (e.g., age-specific cervical cancer incidence and stage-distribution of invasive disease); (ii) the model was calibrated to the most comprehensive population-based data available on HPV, LSIL, HSIL and cancer,<sup>74,75</sup> a process involving systematically varying the input parameters within predetermined ranges such that the model replicated a range of observed outcomes; (iii) an assessment of the calibration was conducted by evaluating the ability of the model to

TABLE I—RANGES USED FOR TRANSITION PROBABILITIES IN MODEL

Variable	Transient HPV <sup>1</sup>	HPV 16/18 <sup>1</sup>	HPV non-16/18 <sup>1</sup>	Low-risk HPV <sup>1</sup>
Natural history parameters for HPV and CIN <sup>10–12,37–47,50–52,57–69</sup>				
Normal to HPV				
<35 years	0.040–0.650	0.027–0.047	0.027–0.047	0.015–0.026
>35 years	0.010–0.025	0.003–0.008	0.003–0.008	0.003–0.008
HPV to LSIL (CIN 1)	0.010–0.046	0.010–0.081	0.010–0.081	0.010–0.046
LSIL (CIN 1) to HSIL (CIN 2/3)	NA	0.080–0.120	0.080–0.120	0.040–0.050
HSIL (CIN 2/3) to CIS				
<30 years	NA	0.010–0.019	0.010–0.019	0.003–0.004
30–39 years	NA	0.010–0.040	0.010–0.040	0.006–0.008
40–49 years	NA	0.050–0.080	0.050–0.080	0.010–0.012
>50 years	NA	0.072–0.114	0.072–0.114	0.020–0.024
HPV clearance	0.137–0.230	0.018–0.234	0.018–0.233	0.018–0.233
LSIL (CIN 1) regression <sup>2</sup>	0.147–0.206	0.062–0.162	0.062–0.162	0.085–0.116
HSIL (CIN 2/3) regression <sup>2</sup>	NA	0.000–0.034	0.000–0.034	0.023–0.113
Progression to invasive cancer <sup>370–73, 75–78</sup>				
CIS to stage I invasive cancer				
13–34 years	NA	0.060–0.090	0.060–0.090	0.060–0.090
35–54 years	NA	0.105–0.150	0.105–0.150	0.105–0.150
55–61 years	NA	0.298–0.596	0.298–0.596	0.298–0.596
>62 years	NA	0.890–0.968	0.890–0.968	0.890–0.968
Stage I invasive cancer				
Progression to stage II	NA	0.137–0.150	0.137–0.150	0.137–0.150
Probability of symptoms	NA	0.047–0.060	0.047–0.060	0.047–0.060
Mortality	NA	0.013–0.014	0.013–0.14	0.013–0.014
Stage II invasive cancer				
Progression to stage III	NA	0.146–0.160	0.146–0.160	0.146–0.160
Probability of symptoms	NA	0.080–0.120	0.080–0.120	0.080–0.120
Mortality	NA	0.029–0.032	0.029–0.032	0.029–0.032
Stage III invasive cancer				
Progression to stage IV	NA	0.206–0.225	0.206–0.225	0.206–0.225
Probability of symptoms	NA	0.200–0.370	0.200–0.370	0.200–0.370
Mortality	NA	0.076–0.084	0.076–0.084	0.076–0.084
Stage IV invasive cancer				
Probability of symptoms	NA	0.225–0.550	0.225–0.550	0.225–0.550
Mortality	NA	0.116–0.176	0.116–0.176	0.116–0.176

<sup>1</sup>Plausible range established using age-specific values where indicated. Estimates are reported as every 6-month probabilities unless otherwise noted. Details of point estimates from calibrated model are available from the authors upon request.<sup>2</sup>LSIL and HSIL can regress to either HPV infection or normal. See Material Methods section.<sup>3</sup>Probabilities for progression through cancer stages and for development of stage-specific symptoms imputed through previously described methods.<sup>24,25,30</sup>—Abbreviations: HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; CIS, carcinoma *in situ*; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

generate reasonable projections of age-specific prevalence curves of HPV, LSIL and HSIL, age-specific cervical cancer incidence and lifetime cancer incidence and mortality that were consistent with published data not used for parameter estimation.<sup>8,76–79</sup>

Data used for the calibration exercises were from a population-based screening study of 9,175 randomly chosen women in a rural province of Costa Rica,<sup>74,75</sup> which provided the best available unbiased estimates of the prevalence of HPV types in all grades of cervical neoplasia. Screening of study subjects included the use of multiple screening tests and comprehensive diagnostic workups to ensure accurate case identification and lesion classification. Specific data used from the study included: age-specific prevalence of HPV infection stratified by type; age-specific prevalence of HPV, LSIL and HSIL; and the distribution of HPV types among women with normal cytology results, histologically-confirmed LSIL, HSIL and cancer (Fig. 1). We assigned priority to calibrating the categories of oncogenic HPV types (HPV-16/18 and HPV non-16/18 or 31, 33, 34, 39, 45, 51, 52, 56, 58, 59, 68) since the appropriate modeling of vaccine effectiveness depends on an accurate representation of this stratification. All remaining infections were reclassified as either low-risk HPV types or transient HPV infection. Based on these data, HPV 16/18 was estimated to be responsible for 61.5% of invasive cervical cancer.

## RESULTS

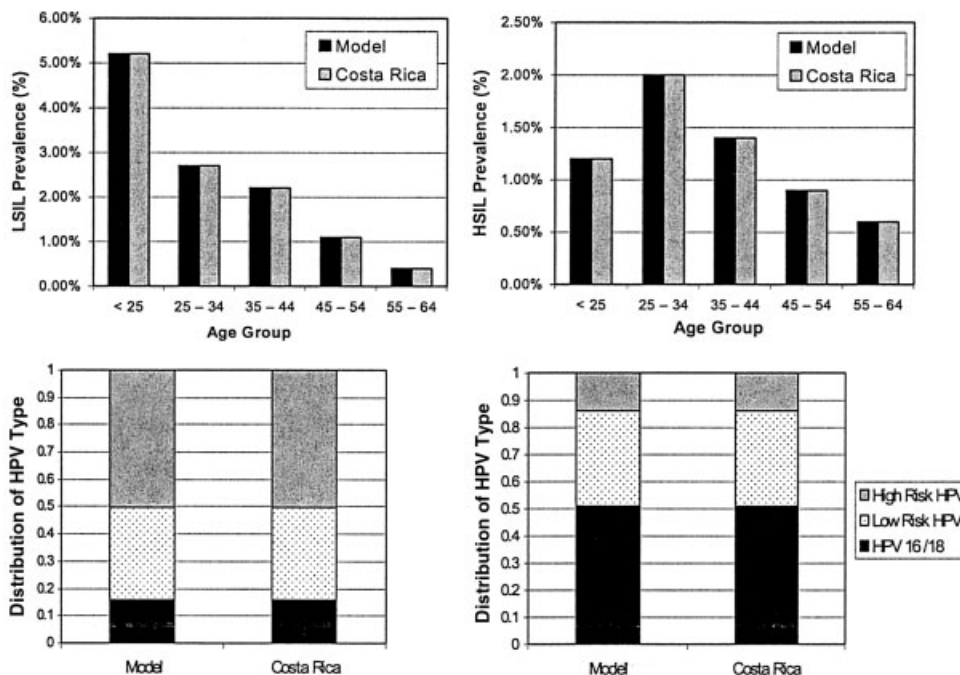
### Predictive capability of the model

The predictive ability of the model was assessed by comparing projected outcomes with data not directly used for calibration. For

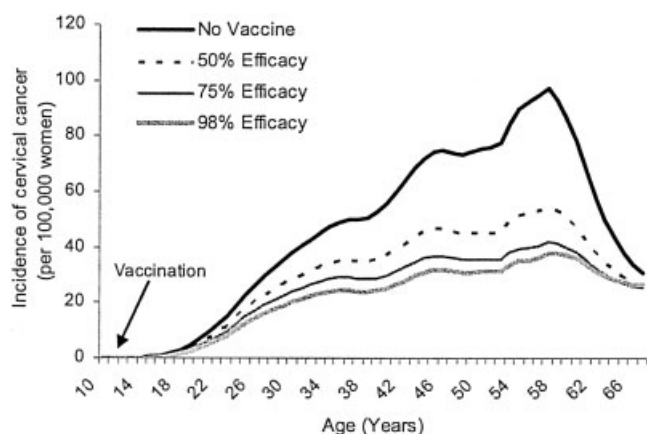
example, the model predicted a peak age-specific cancer incidence of approximately 90 per 100,000 at 59 years of age. In comparison, data from the International Agency for Research on Cancer report a peak cancer incidence at a mean age of 58.8 years for Brazil and many other Latin American regions.<sup>77,78</sup> These results are also consistent with those reported by Gustafsson *et al.*<sup>76</sup> who compared country-specific differences in age-specific cervical cancer incidence curves in 28 unscreened populations. The stage distribution of invasive cancer predicted by the model was similar to that reported for other unscreened populations.<sup>8,79</sup> Finally, the lifetime risk of cancer was 3.7%, similar to published projections using independent models.<sup>57</sup>

### Base case

The impact of vaccines that reduce persistent HPV-16/18 infection rates by 50%, 75% and 98% on the annual incidence of cervical cancer is illustrated in Figure 2. The cumulative reduction in cervical cancer cases, stratified by HPV type, is shown in Figure 3a. A vaccine that prevented 98% of persistent HPV 16/18 was associated with an approximate equivalent reduction in persistent HPV-16/18-associated cancer and a 51% reduction in total cancer (i.e., cancer caused by any high-risk HPV type). Under the base case assumptions, the model predicted an “amplified” benefit in the reduction in HPV-16/18-associated cervical cancer with a partially effective vaccine (e.g., a vaccine that prevented 75% of persistent HPV 16/18 was associated with an 85% reduction in persistent HPV-16/18-associated cancer) but an “attenuated” effect with respect to the reduction of total cancer cases (e.g., a vaccine that



**FIGURE 1** – Age-specific prevalence of LSIL and HSIL projected by the model after calibration to data from the population-based screening study in Costa Rica (top panel). The distribution of HPV types among women with biopsy-confirmed LSIL and HSIL from these data are compared to the distribution projected by the model (bottom panel). HPV types are categorized as follows: non-16/18 high-risk HPV (referred to as High Risk HPV in figure), low-risk HPV and HPV 16/18.



**FIGURE 2** – Impact of HPV-16/18 vaccines on incidence of cervical cancer. Age-specific cancer incidence is predicted for vaccines that reduce the incidence of persistent HPV-16/18 infection by 50%, 75% and 98%, where women are immunized by model entry at age 13 years.

prevented 75% of persistent HPV 16/18 was associated with a 44% reduction in all cancers).

These discordant observations are a result of the following assumptions. To model partial vaccine efficacy, we assumed the vaccine reduced the probability of developing persistent infection with HPV 16/18 by a specified amount in every woman in the cohort. If a woman cleared a persistent HPV infection, she faced the possibility of developing another persistent HPV infection with the same HPV type. Accordingly, she also continued to benefit from a probable reduction in her cancer risk due to vaccination. This assumption resulted in an amplified benefit with respect to the reduction in cumulative HPV-16/18-associated cancers.

A second assumption resulted in an attenuated effect on the reduction of total cancer cases, partially blunting the amplification effect noted above. We assumed that women in whom persistent HPV-16/18 infection was successfully prevented were subject to the competing risks associated with acquisition of other HPV

types. The implications of this ongoing susceptibility to non-16/18 HPV types are shown in Figure 3a. As expected, there was a reduction in HPV-16/18 associated cancers with effective vaccination. However, the cumulative number of cancers due to other HPV types actually increased. The impact of this assumption is greater at higher vaccine efficacies, since a relatively greater proportion of women are eligible to acquire infection with other HPV types.

Although our primary outcome of concern is reduction of cervical cancer cases and deaths, the impact of vaccination on surrogate markers and intermediate outcomes has implications for designing clinical trials and assessing the impact of vaccination on screening practices. Figure 3 shows that the compensatory increase in non-HPV-16/18-cancer associated outcomes, accompanying the vaccine-attributable reduction in HPV-16/18 cancer outcomes, was also observed with respect to HSIL (Fig. 3b) and most pronounced with respect to LSIL. In fact, the reduction in HPV-16/18-associated LSIL was nearly completely offset by increases in LSIL attributable to other HPV types. This is potentially a reflection of the fact that LSIL is essentially a manifestation of HPV infection rather than a step in the critical pathway to cancer, and is therefore less tightly associated with high-risk persistent HPV-16/18 infection. (Fig. 3c)

A valuable attribute of simulation models is the ability to project long-term outcomes under a variety of alternative assumptions when empiric data are lacking. These exploratory simulations can be valuable in demonstrating where the acquisition of definitive data may be the most influential. Figure 4 shows the projected reduction in total cervical cancer in 2 hypothetical scenarios that reflect alternative assumptions about the competing risk of non-16/18 cancers in women successfully vaccinated against HPV 16/18. The lower dashed curve (competing risk) represents the projected reduction in cancer assuming that women successfully vaccinated against HPV 16/18 are eligible to become infected with non-16/18 types, resulting in a compensatory increase in non-16/18-associated outcomes. The upper solid curve (no competing risk) represents the projected reduction in cancer assuming that women destined for HPV 16/18-associated invasive cancer, and then protected due to successful 16/18 vaccination, are not eligible for non-16/18 HPV infections. Figure 5 shows the implications of different coverage rates on the projected outcomes of an HPV-

16/18 vaccine. Regardless of the baseline vaccine efficacy, the proportion of the cohort successfully vaccinated is a critical determinant of total cancer reduction. The difference in baseline vaccine efficacy is most influential when vaccine coverage rates approach 100%.

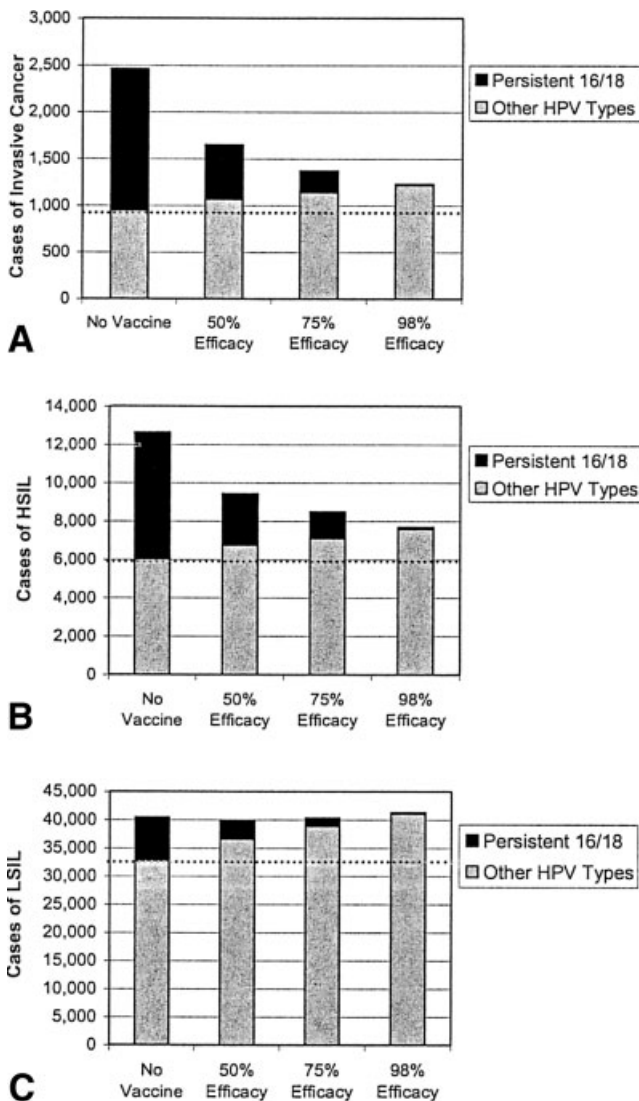
The proportion of persistent HPV infection observed in older women that is attributable to latent or previously acquired infections vs. new HPV infections is uncertain. Under 3 alternative assumptions about the natural history model, we explored the impact of waning immunity in older women who were previously vaccinated. Figure 6 shows the projected reduction in overall invasive cervical cancer with 3 HPV-16/18 vaccines (efficacy of 50%, 75% and 98% against persistent HPV 16/18) whose efficacy wanes 10 years after vaccination by a factor of 25% to 100%. The

3 panels in Figure 6 reflect 3 different assumptions about the proportion of persistent HPV infection in women over the age of 30 attributable to latent or previously acquired infections vs. new infections. As the proportion of persistent HPV infections in older women attributable to new infections (vs. latent or previously acquired infections) is increased, the relative effect of waning is greater. Figure 6a depicts the assumption that 50% of persistent HPV infection in older women is attributable to latent (i.e., previously acquired) infections and 50% is attributable to new infections.

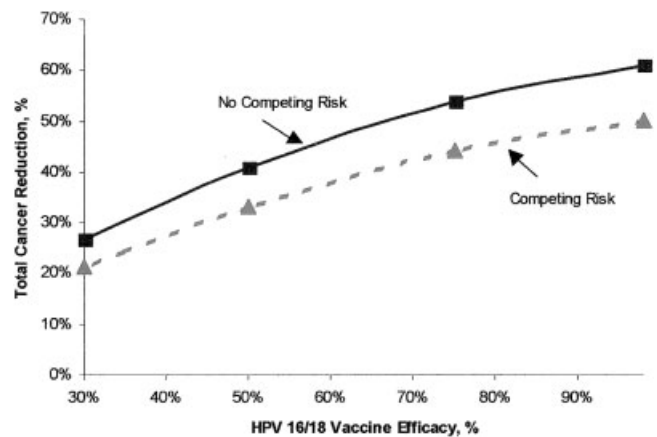
DISCUSSION

Decisions related to both clinical study design and health policy must often be made in the face of uncertainty. Although there are substantial data supporting the causative role of persistent HPV infection in the development of cervical cancer, the complete course of disease, from acquisition of HPV to the development of invasive cancer, has never been and will never be completely observed. This fact challenges clinical investigators, health policy analysts and public health decision-makers to determine appropriate courses of action based on the best available clinical and epidemiologic data.

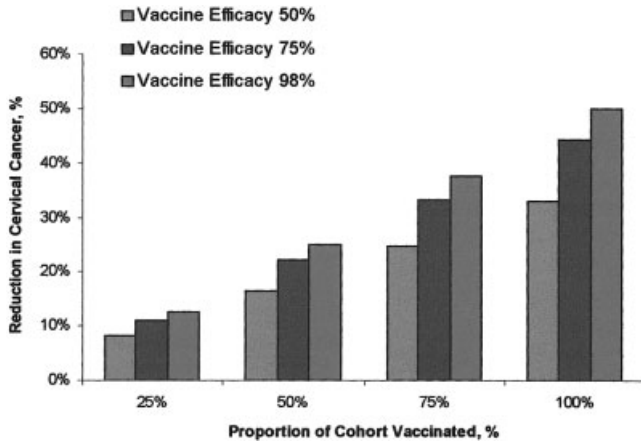
Several cervical cancer models have been developed to assess the costs and/or benefits of screening for cervical cancer.<sup>23,24</sup> They have provided important groundwork for thinking about the modeling structure and data requirements necessary to evaluate HPV testing. To evaluate the impact of a type-specific HPV vaccine, however, a more detailed model is required, one that is capable of simulating the entire natural history of cervical disease conditional on HPV type. To our knowledge, there have been no such models calibrated simultaneously to age-specific prevalence of HPV, LSIL, HSIL and cervical cancer and to the distribution of HPV types across the spectrum of cervical disease. The results of our calibration exercise demonstrate: a reasonable visual fit to age-specific prevalence rates for all precancerous lesions compared to the Costa Rica population study; accurate and reproducible estimates for the age-specific incidence and lifetime cumulative incidence of cervical disease compared to data from unscreened pop-



**FIGURE 3** – Impact of HPV-16/18 vaccines on projected cases of invasive cancer (a), HSIL (b) and LSIL (c) by HPV type. Reductions in HPV-16/18-associated cancer and HSIL are accompanied by small increases in non-16/18-associated cancer and HSIL due to the competing risks of other high-risk HPV types. Reductions in HPV-16/18-associated LSIL are completely offset by increases in LSIL attributable to other HPV types. Other HPV types include transient infection with any HPV type, persistent low-risk HPV types and persistent non-16/18 high-risk HPV types. The dotted line indicates the level of cancer, HSIL and LSIL cases attributable to other HPV types in the absence of vaccination. See Results section for details.



**FIGURE 4** – Impact of alternative assumptions about the competing risk of non-16/18 HPV associated cancer in women vaccinated against HPV 16/18. Percent reduction in cases of cervical cancer compared to an unvaccinated cohort is examined as a function of vaccine efficacy using 2 different assumptions. The lower dashed curve (competing risk) represents the projected reduction in cancer assuming that women successfully vaccinated against HPV 16/18 are eligible to become infected with non-16/18 types. The upper solid curve (no competing risk) represents the projected reduction in cancer assuming that women destined for HPV-16/18-associated invasive cancer, and then protected due to successful 16/18 vaccination, are not eligible for non-16/18 HPV infections.



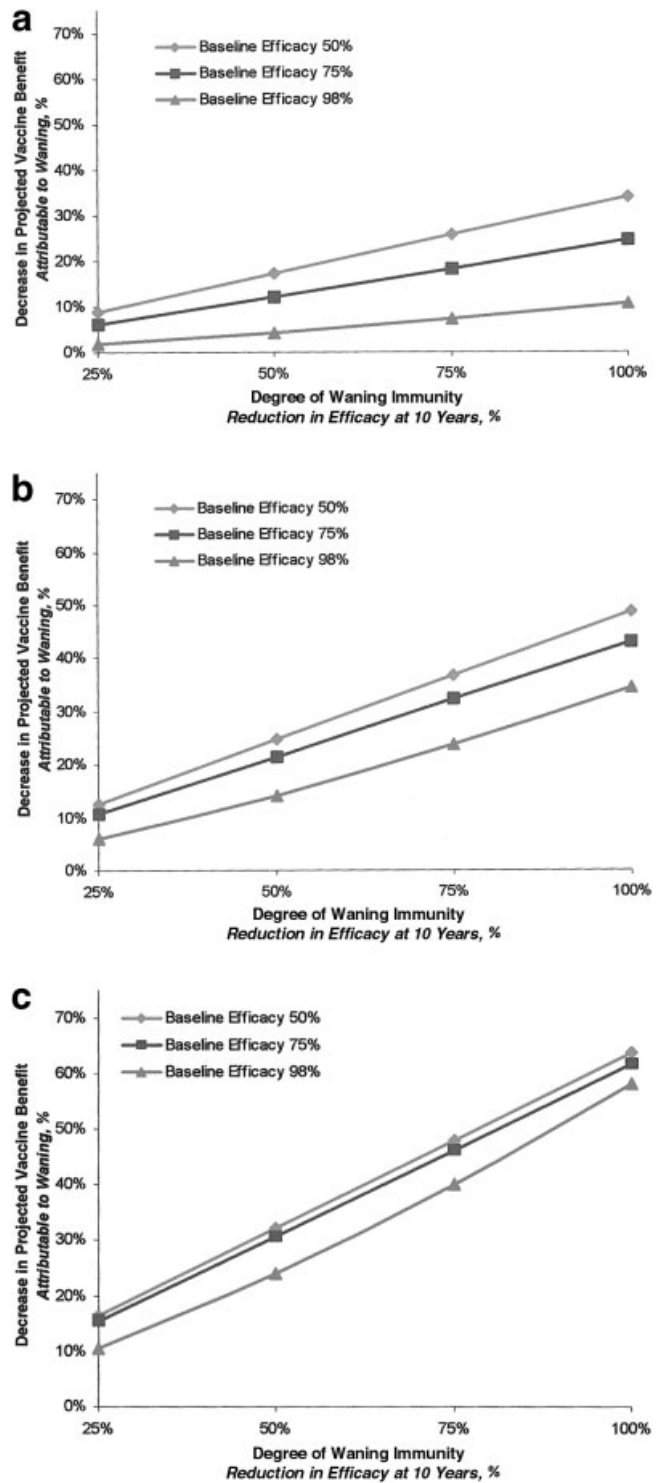
**FIGURE 5** – Impact of HPV-16/18 vaccine coverage rates on projected reduction of invasive cervical cancer. For 3 hypothetical vaccines that prevent 50% (right bars), 75% (middle bars) and 98% (left bars) of persistent HPV 16/18, the proportion of the cohort successfully vaccinated is varied from 25% to 100%. The difference in baseline vaccine efficacy is most influential at higher vaccine coverage rates.

ulations; and a reproducible representation of type-specific HPV within each stage of cervical disease, from LSIL to invasive cancer. The ability to calibrate such a complex model to multiple outcomes both longitudinally and cross-sectionally provides qualitative support (although not epidemiologic evidence) for the underlying assumption regarding the role of persistent HPV infection in the development of cancer. For example, if cervical cancer does not occur through persistent HPV infection, but through some as yet unidentified alternative pathway, the model would not be likely to project all intermediate outcomes accurately and simultaneously.

In the base case scenario, we found that a partially effective vaccine had a magnified effect on the reduction of HPV-16/18-associated cancer and an attenuated effect on total cancer cases due to assumptions we made in modeling vaccine efficacy. As recommended by the Panel on Cost-Effectiveness in Health and Medicine,<sup>19</sup> we conducted additional analyses to explore the impact of several alternative assumptions with respect to the nature of vaccine efficacy, the degree of waning immunity and the extent to which competing risk due to other HPV types plays a role in women who are vaccinated against HPV 16/18.

Such simulations are meant to be exploratory and can assist in identifying and prioritizing areas where the acquisition of empiric data may be most influential. For example, despite divergent assumptions about the risk of competing non-16/18 HPV types in women vaccinated against HPV 16/18, the reduction in invasive cervical cancer remained substantial. On the other hand, assumptions about the proportion of the at-risk population successfully vaccinated had dramatic impact on the estimated benefits of HPV-16/18 vaccination. It is clear that broad population coverage (e.g., at least 75% of the at-risk cohort) with a partially effective vaccine that prevents 50% to 75% of persistent HPV 16/18 will provide a greater reduction in cervical cancer than coverage of less than 50% of the at-risk cohort with a very effective vaccine that prevents 98% of persistent HPV 16/18.

A better understanding of what proportion of persistent HPV infections that eventually lead to cancer are a result of reactivation of latent or previously acquired HPV as opposed to new incident infections acquired later in life will substantially affect the consequences of waning immunity with respect to HPV-16/18 vaccination. At one extreme, if the majority of cervical cancer in 50-year-old women is a result of new HPV infections that are acquired after age 25 or 30, administering a vaccine to a 12-year-old girl that



**FIGURE 6** – Impact of waning immunity at 10 years according to baseline vaccine efficacy. The reduction is projected in overall invasive cervical cancer with 3 HPV-16/18 vaccines (efficacy of 50%, 75% and 98% against persistent HPV 16/18) whose efficacy wanes 10 years after vaccination by a factor of 25% to 100%. (a) The upper panel assumed that 100% of persistent HPV infections in older women are attributable to latent or previously acquired infections. (b) The middle panel assumed the proportion of persistent HPV infections in women over the age of 30 attributable to latent or previously acquired infections is 50%, and the proportion attributable to new infections is 50%. (c) The lower panel assumed that 100% of persistent HPV infections are attributable to newly acquired infections.

wanes after 10 or 15 years will have a markedly reduced impact on the prevention of cervical cancer. At the other extreme, if the majority of cervical cancers are caused by reactivation of latent or previously acquired HPV earlier in life, then an HPV-16/18 vaccine administered to a 12-year-old girl that is effective during the 10 to 15 years she is at highest risk for incident HPV infections may still have a substantial effect on cervical cancer. We felt it prudent to present the projected results for both of these extreme assumptions, as well as one which assumed approximately half of persistent HPV infections in older women are attributable to new infections and half attributable to reactivation of latent or previous HPV infections acquired earlier in life.

There are a number of limitations that should be highlighted:

1. It is well documented that the proportion of invasive cancer attributable to HPV 16/18 varies between different regions of the world.<sup>14,15</sup> Since the natural history model is calibrated to data from Costa Rica, caution should be used in generally applying this data to other regions. If the prevalence of HPV 16/18 and the proportion of cervical cancer due to HPV 16/18 is higher than we assumed in our base case, we may have underestimated the benefits of vaccination.

2. The age-specific prevalence of HPV varies with the age of onset of sexual activity, patterns of sexual behavior, other risk factors (e.g., oral contraceptives and smoking), as well as the sensitivity of the assay.<sup>80–82</sup>

3. Since the relative reduction in LSIL with a type-specific vaccine is a function of the proportion of precursor lesions attributable to HPV 16/18, there is a greater reduction in the projected age-specific prevalence of HSIL than LSIL for Costa Rica, but this may not be observed in other areas of the world. Region-specific analyses should be conducted that take these factors into account.

4. The average age at which peak annual incidence of invasive cancer occurs, the stage-distribution and stage-specific mortality rates will vary with geographic location, level of health care infrastructure and level of cytology screening. The causal pathway of cervical carcinogenesis and the role of persistent HPV would not be expected to differ despite these differences. In fact, by adjusting for local factors (sexual activity patterns, distribution of HPV types in SIL and cancer and screening practice), the model is adaptable to forecasting vaccine benefits in other settings.

5. We have implicitly assumed that the majority of persistent HPV infections in older women represent reactivation of latent or previously acquired HPV. Assumptions about the relative proportion of persistent HPV infections in women over the age of 30 attributable to new exposure and acquisition of HPV as opposed to reactivation of latent or previously acquired HPV will have an important impact on the projected clinical effects of waning. Empiric data to inform these assumptions are of highest priority.

6. Our model is not a transmission model, and to assess the impact of HPV vaccination of males and females on the transmission of disease, epidemic models will be required.<sup>83</sup> Dynamic models that allow people to enter or exit the model over time are more suitable for evaluating disease trends over time and will be necessary to monitor vaccination programs after they are implemented. Finally, there are heterogeneities in vaccine response that we did not include in the absence of empiric data.

Future health policy initiatives that involve both screening and vaccination will need to anticipate the possible impact of vaccination on the screening program. For example, if an HPV-16/18 vaccine is associated with a reduction in SIL prevalence, there could be health economic benefits resulting from lower associated screening costs.<sup>84</sup> On the other hand, if vaccination has relatively less impact on the most common lesion, namely LSIL, then the cost-effectiveness of vaccination in a country with screening will be very sensitive to current screening practices and their ability to shift, in the context of a vaccine program. Our study highlights the importance of getting better information on the age-related distribution of HPV types within LSIL and HSIL, the regional variation of these distributions in different parts of the world, the attributable risk posed by non-16/18 HPV types in women successfully immunized against HPV 16/18 and the degree of potential cross protection that might occur with a type-specific HPV vaccine. These types of studies do not all need to be experimental, but may be observational. By combining the powers of mathematical modeling with those of randomized controlled trials, we can achieve more than with each in isolation.

Our results show that a prophylactic vaccine that prevents persistent HPV-16/18 infection can be expected to significantly reduce HPV-16/18-associated HSIL and cervical cancer. Despite examining several divergent assumptions that resulted in amplification or blunting of the vaccine's effect on outcomes, a vaccine that is 75% effective in reducing persistent HPV-16/18 infection can be expected to prevent 70% to 83% of HPV-16/18 cancer cases. The impact on overall prevalence of HPV or LSIL, however, may be less pronounced. Based on the relative importance of different parameters in the model, important priorities for future research and public health policy include understanding the heterogeneity of vaccine response, effect of type-specific vaccination on other HPV types and degree to which vaccination effect persists over time.

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#### REFERENCES

1. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 64. Human Papillomaviruses. Lyon, France: International Agency for Research on Cancer. 1995.
2. Schiffman M. New epidemiology of human papillomavirus infection and cervical neoplasia. *J Natl Cancer Inst.* 1995;87:1345–1347.
3. Franco EL, Rohan TE, Villa LL. Epidemiologic evidence and human papillomavirus infection as a necessary cause of cervical cancer. *J Natl Cancer Inst.* 1999;91:506–11.
4. Pisani P, Parkin D, Munoz N, Ferlay J. Cancer and infection: estimates of the attributable fraction in 1990. *Cancer Epidemiol Biomarkers and Prev* 1997;6:387–400.
5. Sankaranarayanan R, Black RJ, Swaminathan R, Parkin DM. An overview of cancer survival in developing countries. *IARC Sci Publ* 1998;145:135–173.
6. Pisani P, Parkin DM, Bray F, Ferlay J. Estimates of the worldwide mortality from 25 cancers in 1990. *Int J Cancer.* 1999;83:18–29.
7. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. *Int J Cancer.* 1999;80:827–41.
8. Ponten J, Adami HO, Bergstrom R, Dillner J, Friberg LG, Gustafsson L, Miller AB, Parkin DM, Soren P, Trichopoulos D. Strategies for global control of cervical cancer. *Int J Cancer.* 1995; 60:1–26.
9. Current status of development of prophylactic vaccines against human papillomavirus infection. Report of a technical meeting, Geneva, 16–18 February 1999. Department of Vaccines and other Biologicals, World Health Organization, and the International Agency for Research on Cancer, Geneva 1999. Available at [www.who.int/gpv-documents/](http://www.who.int/gpv-documents/)
10. Schlecht NF, Kulaga S, Robitaille J, Ferreira S, Santos M, Miyamura RA, Duarte-Franco E, Rohan TE, Ferenczy A, Villa LL, Franco EL. Persistent human papillomavirus infection as a predictor of cervical intraepithelial neoplasia. *JAMA.* 2001; 286:3106–3114.
11. Moscicki AB, Hills N, Shiboski S, Powell K, Jay N, Hanson E, Miller S, Clayton L, Farhat S, Broering J, Darragh T, Palefsky J. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesions development in young females. *JAMA.* 2001; 285:2995–3002.
12. Woodman CB, Collins S, Winter H, Bailey A, Ellis J, Prior P, Yates M, Rollason TP, Young LS. Natural history of cervical human pap-

- illomavirus infection in young women: a longitudinal cohort study. *Lancet* 2001;357:1831–1836.
13. Ferenczy A, Franco EL. Persistent human papillomavirus infection and cervical neoplasia. *Lancet Oncol*. 2002;3:11–16.
  14. Walboomers J, Jacobs M, Manos M, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ, Munoz N. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12–19.
  15. Bosch F, Manos M, Munoz N, Sherman M, Jansen AM, Peto J, Schiffman MH, Moreno V, Kurman R, Shah KV. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. *J Natl Cancer Inst*. 1995;87(11):796–802.
  16. Galloway DA. Is vaccination against human papillomavirus a possibility? *Lancet* 1998;351 (suppl III):22–24. 1998
  17. Lowy DR, Schiller JT. Papillomaviruses: prophylactic vaccine prospects. *Biochimica et Biophysica Acta* 1998;1423:M1–M8. 1998
  18. Koutsky LA, Ault K, Wheeler CM, Brown DR, Barr E, Alvarez FB, Chiacchierini LM, Jansen KU. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med*. 2002;347:1645–51.
  19. Gold MR, Siegel JE, Russel LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Pr; 1996.
  20. Halpern MT, Luce BR, Brown RE, Geneste B. *Health and Economic Outcomes Modeling Practices: A Suggested Framework*. Value in Health. 1998;2:131–147.
  21. Weinstein MC, Toy EL, Sandberg EA, Neumann PJ, Evans JS, Kuntz KM, Graham JD, Hammit JK. Modeling for health care and other policy decisions: Uses, Roles and Validity. Value in Health. 2001;4: 348–361.
  22. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute for Clinical Excellence (NICE). *Lancet* 2002;360:711–15.
  23. Schatzkin A. Intermediate markers as surrogate endpoints in cancer research. *Hematol Oncol Clin North Am* 2000; 4:887–905.
  24. Goldie SJ, Weinstein MC, Kuntz KM, Freedberg KA. The costs, clinical benefits, and cost-effectiveness of screening for cervical cancer in HIV-infected women. *Ann Intern Med*. 1999;130:97–107.
  25. Goldie SJ, Kuhn L, Denny L, Pollack, Wright TC. Policy analysis of cervical cancer screening strategies in low-resource settings: clinical benefits and cost-effectiveness. *JAMA* 2001;285(24):3107–3115.
  26. Sherlaw-Johnson C, Gallivan S, Jenkins D. Evaluating cervical cancer screening programmes for developing countries. *Int J Cancer*. 1997; 72(2):210–216.
  27. Jenkins D, Sherlaw-Johnson C, Gallivan S. Can papilloma virus testing be used to improve cervical cancer screening? *Int J Cancer* 1996;65(6):768–773.
  28. van Ballegooijen M, van den Akker-van Marle ME, Warmerdam PG, Meijer CJ, Walboomers JM, Habbema JD. Present evidence on the value of HPV testing for cervical cancer screening: a model-based exploration of the (cost-) effectiveness. *Br J Cancer*. 1997;76(5):651–657.
  29. Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, van Ballegooijen M, van den Akker E. A systematic review of the role of human papillomavirus testing within a cervical screening programme. *Health Technol Assess*. 1999;3:14.
  30. Myers E, McCrory D, Nanda K, Matchar D. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *Am J Epidemiol*. 2000;151:1158–1171.85.
  31. Brown AD, Garber AM: Cost-effectiveness of 3 methods to enhance the sensitivity of Papanicolaou testing. *JAMA*. 1999; 281:347–353.
  32. Eddy DM. Screening for cervical cancer. *Ann Intern Med*. 1990;113: 214–226.
  33. Fahs MC, Mandelblatt J, Schechter C, Muller C. Cost effectiveness of cervical cancer screening for the elderly. *Ann Intern Med*. 1992;117: 520–527.
  34. van der Akker-van Marle ME, van Ballegooijen M, van Oortmarssen GJ, Boer R, Habbema JD. Cost-effectiveness of cervical cancer screening: comparison of screening policies. *J Natl Cancer Inst*. 2002; 94:193–204.
  35. Pecorelli S, Benedet JL, Creasman WT, Shepherd JH. FIGO staging of gynecologic cancer. 1994-1997 FIGO Committee on Gynecologic Oncology. International Federation of Gynecology and Obstetrics. In. *J Gynaecol. Obstet*. 1999;65:243–9.
  36. Wallin KL, Wiklund F, Angstrom T, Bergman F, Stendahl U, Wadell G, Hallmans G, Dillner J. Type-specific persistence of human papillomavirus DNA before the development of invasive cervical cancer. *N Engl J Med* 1999;341(22):1633–1638.
  37. Noppenhuis MA, Walboomers JM, Helmerhorst TJ, Rozendaal L, Remmink AJ, Risse EK, van der Linden HC, Voorhorst FJ, Kenemans P, Meijer CJ. Relation of human papillomavirus status to cervical lesions and consequences for cervical cancer screening: a prospective study. *Lancet*. 1999;354:20–25.
  38. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med*. 1998;338:423–8.
  39. Remmink AJ, Walboomers JM, Helmerhorst TJ, Voorhorst FJ, Rozendaal L, Risse EK, Meijer CJ, Kenemans P. The presence of persistent high-risk HPV genotypes in dysplastic cervical lesions is associated with progressive disease:natural history up to 36 months. *Int J Cancer*. 1995;61:306–311.
  40. Ellerbrock TV, Chiasson MA, Bush TJ, Sun XW, Sawo D, Brudney K, Wright TC. Incidence of cervical squamous intraepithelial lesions in HIV-infected women. *JAMA*. 2000;283(8):1031–1037.
  41. Londesborough P, Ho L, Terry G, Cuzick J, Wheeler C, Singer A. Human papillomavirus genotype as a predictor of persistence and development of high-grade lesions in women with minor cervical abnormalities. *Int J Cancer*. 1996;69:364–8.
  42. Rozendaal L, Walboomers JM, van der Linden JC, Voorhorst FJ, Kenemans P, Helmerhorst TJ, van Ballegooijen M, Meijer CJ. PCR-based high-risk HPV test in cervical cancer screening gives objective risk assessment of women with cytomorphologically normal cervical smears. *Int J of Cancer*. 1996;68:766–769.
  43. Ho G, Burk R, Klein S, Kadish AS, Chang CJ, Balan P, Basu J, Tachezy R, Lewis R, Romney S. Persistent genital human papillomavirus infection as a risk factor for persistent cervical dysplasia. *J Natl Cancer Inst*. 1995;87(18):1365–1371.
  44. Hildesheim A, Schiffman MH, Gravitt PE, Glass AG, Greer CE, Zhang T, Scott DR, Rush BB, Lawler P, Sherman ME, Kurman RG, Manos MM. Persistence of type-specific human papillomavirus infection among cytologically normal women. *J Infect Dis*. 1994;169:235–240.
  45. Koutsky LA, Holmes KK, Critchlow CW, Stevens CE, Paavonen J, Beckmann AM, DeRouen TA, Galloway DA, Vernon D, Kiviat NB. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. *N Engl J Med*. 1992;327: 1272–1278.
  46. Rousseau MC, Pereira JS, Prado JCM, Villa LL, Rohan TE, Franco EL. Cervical coinfection with human papillomavirus (HPV) types as a predictor of acquisition and persistence of HPV infection. *J Infect Dis* 2001;184:1508–17.
  47. Franco E, Villa L, Rohan T, Ferenczy A, Petzl-Erler M, Matlashewski G. Design and methods of the Ludwig-McGill longitudinal study of the natural history of human papillomavirus infection and cervical neoplasia in Brazil. *Rev Panam Salud Publica*. 1999;6(4):223–33
  48. The 1988 Bethesda System for reporting cervical/vaginal cytological diagnoses. National Cancer Institute Workshop. *JAMA*. 1989;262: 931–4.
  49. Luff RD. The Bethesda System for reporting cervical/vaginal cytologic diagnoses: report of the 1991 Bethesda workshop. The Bethesda System Editorial Committee. *Hum Pathol*. 1992;23(7):719–721.
  50. Franco E, Villa L, Sobrinho J, Prado JM, Rousseau MC, Desy M, Rohan TE. Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. *J Infect Dis* 1999;180:1415–1423.
  51. Moscicki AB, Shiboski S, Broering J, Powell K, Clayton L, Jay N, Darragh TM, Brescia R, Kanowitz S, Miller SB, Stone J, Hanson E, Palefsky J. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. *J Pediatrics*. 1998;132(2):277–284.
  52. Sun XW, Kuhn L, Ellerbrock TV, Chiasson MA, Bush TJ, Wright TC. Human papillomavirus infection in women infected with the human immunodeficiency virus. *N Engl J Med* 1997;37:1343–9.
  53. Walboomers JMM, Meijer CJLM. Do HPV-negative cervical carcinomas exist? *J Pathol* 1997; 181:253–7.
  54. Franco EL. Measurement errors in epidemiological studies of human papillomavirus an cervical cancer. *IARC Sci Publ*; 119:181–97.
  55. Franco EL. Statistical issues in human papillomavirus testing and screening. *Clinics in Laboratory Med*. 2000;20:346–367.
  56. World Health Organization Statistical Information System (WHOSIS). 1997 – 1999 World Health Statistics Annual. Available: <http://www-nt.who.int/whosis/statistics/menu.cfm> (Accessed July 2001)
  57. McCrory D, Mather D, Bastain L, Datta S, Hasselblad V, Hickey J, Myers E, Nanda K. Evaluation of Cervical Cytology. Evidence Report/Technology Assessment No.5 (Prepared by Duke University under Contract No. 290-97-0014). AHCPR Publication No. 99-E010. Rockville, MD: Agency for Health Care Policy and Research. February 1999. Available: <http://www.ahrq.gov/clinic/epcsums/cervsumm.htm>
  58. Hopman EH, Rozendaal L, Voorhorst FJ, Walboomers JM, Kenemans P, Helmerhorst TJ. High risk human papillomavirus in women with normal cervical cytology prior to the development of abnormal cytology and colposcopy. *Br J Obstet Gynaecol* 2000; 107: 600–604.
  59. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol*. 1993;12(2):186–192.
  60. Melnikow J, Nuovo J, Willan AR, Chan BK, Howell LP. Natural

- history of cervical squamous intraepithelial lesions: a meta-analysis. *Obstet Gynecol.* 1998;92(4 Pt 2):727-735.
61. Holowaty P, Miller AB, Rohan T, To, T. Natural history of dysplasia of the uterine cervix. *J Nat Cancer Instit* 1999; 91: 252 - 258.
  62. Syrjanen K, Kataja V, Yliskoski M, Chang F, Syrjanen S, Saarikoski S. Natural history of cervical human papillomavirus lesions does not substantiate the biologic relevance of the Bethesda System. *Obstet Gynecol* 1992; 79: 675 - 682.
  63. Burk RD, Kelly P, Feldman J, Bromberg J, Vermund SH, DeHovitz JA, Landesman SH. Declining prevalence of cervicovaginal human papillomavirus infection with age is independent of other risk factors. *Sex Transm Dis.* 1996;23:333-341.
  64. Melkert PJ, Hopman E, van den Brule J, Risse E, Van Diest P, Bleker O. Prevalence of HPV in cytologically normal cervical smears, as determined by the polymerase chain reaction, is age-dependent. *Int J Cancer.* 1993;53:919-923.
  65. Bauer HM, Hildesheim A, Schiffman MH, Glass AG, Rush BB, Scott DR, Cadell DM, Kurman RJ, Manos MM. Determinants of genital human papillomavirus infection in low-risk women in Portland, Oregon. *Sex Transm Dis.* 1993;20(5):274-278.
  66. Kotloff KL, Wasserman SS, Russ K, Shapiro S, Daniel R, Brown W, Frost A, Tabaro SO, Shah K. Detection of genital human papillomavirus and associated cytological abnormalities among college women. *Sex Transm Dis* 1998;25:243-250.
  67. Liaw K, Glass AG, Manos MM, Greer CE, Scott DR, Sherman M, Burk RD, Kurman RJ, Wacholder S, Rush BB, Cadell DM, Lawler P, Tabor D, Schiffman M. Detection of human papillomavirus DNA in cytologically normal women and subsequent cervical squamous intraepithelial lesions. *J Natl Cancer Inst.* 1999;91:954-960.
  68. Liu T, Soong SJ, Alvarez RD, Butterworth CE. A longitudinal analysis of human papillomavirus 16 infection, nutritional status, and cervical dysplasia progression. *Cancer Epidemiology, Biomarkers, and Prevention.* 1995;4:373-380.
  69. Nasiell K, Roger V, Nasiell M. Behavior of mild cervical dysplasia during long-term follow-up. *Obstet Gynecol* 1986;67:665-669.
  70. Pretorius R, Semrad N, Watring W, Fotheringham N. Presentation of cervical cancer. *Gynecol Oncol* 1991; 42: 48 - 53.
  71. Surveillance, Epidemiology, End Results (SEER) Cancer Statistics Review, 1973-1994. US Dept of Health and Human Services, PHS, NIH, NCI, Bethesda, Maryland. SEER Home Page, <http://www-seer.ims.nci.nih.gov/>; National Cancer Institute; 1997.
  72. Robles SC, White F, Peruga A. Trends in cervical cancer mortality in the Americas. *Bull Pan AM Health Organ* 1996; 30 (4): 290 - 301.
  73. Ferlay J, Bray F, Pisani P, Parkin D. GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0. IARC CancerBase No. 5. Lyon, IARC Press, 2001.
  74. Herrero R, Schiffman MH, Bratti C, Hildesheim A, Balmaceda I, Sherman ME, Greenberg M, Cardenas F, Gomez V, Helgesen K, Morales, J, Hutchinson M et al. Design and methods of a population-based natural history study of cervical neoplasia in a rural province of Costa Rica: the Guanacaste Project. *Rev Panam Salud Publica.* 1997; 1:362-75.
  75. Herrero R, Hildesheim A, Bratti C, Sherman ME, Hutchinson M, Morales J, Balmaceda I, Greenberg MD, Alfaro M, Burk RD, Wacholder S, Plummer M, Schiffman M. Population-based study of human papillomavirus infection and cervical neoplasia in rural Costa Rica. *J Natl Cancer Inst.* 2000;92(6):464-474.
  76. Gustafsson L, Ponten J, Bergstrom R, Adami HO. International incidence rates of invasive cervical cancer before cytological screening. *Int J Cancer* 1997;71(2):159-165.
  77. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J (Eds.) *Cancer Incidence in Five Continents Vol. VII.* International Agency for Research on Cancer Scientific Publications No. 143. IARC 1997; Lyon, France.
  78. Sierra R, Barrantes R, Munoz Leiva G, Parkin D, Bieber C, Munoz C. *Cancer in Costa Rica.* International Agency for Research on Cancer Technical Report No. 1. 1998: Lyon France.
  79. Fidler HK, Boyes DA, Worth AJ. Cervical cancer detection in British Columbia: A progress report. *J Obstet Gynaec Brit Cwltb* 1968; 75:392-404.
  80. Rousseau MC, Franco EL. A cumulative case-control study of risk factor profiles for oncogenic and nononcogenic cervical human papillomavirus infections. *Cancer Epidemiol Biomarkers Prev.* 2000; 9:469-76.
  81. Castle PE, Schiffman M, Gravitt PE, Kendall H, Fishman S, Dong H, Hildesheim A, Herrero R, Bratti M, Sherman M, Lorincz A, Schussler J, Burk RD. Comparisons of HPV DNA detection by MY09/11 PCR Methods. *Journal of Medical Virology.* 2002; 68:417-423.
  82. Castle PE, Schiffman M, Burk RD, Wacholder S, Hildesheim A, Herrero R, Bratti MC, Sherman ME, Lorincz A. Restricted Cross-Reactivity of Hybrid Capture 2 with Nononcogenic Human Papillomavirus Types. *Cancer Epidemiology, Biomarkers, and Prevention.* 2002; 11:1394-1399
  83. Highes JP, Garnett GP, Koutsky LA. The theoretical population level impact of a prophylactic human papillomavirus vaccine. *Epidemiol* 2002;13:631-9.
  84. Sanders G, Taira AI. Cost effectiveness of a potential vaccine for human papillomavirus. *Emerging Infectious Diseases.* 2003; 9:37-48.