

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

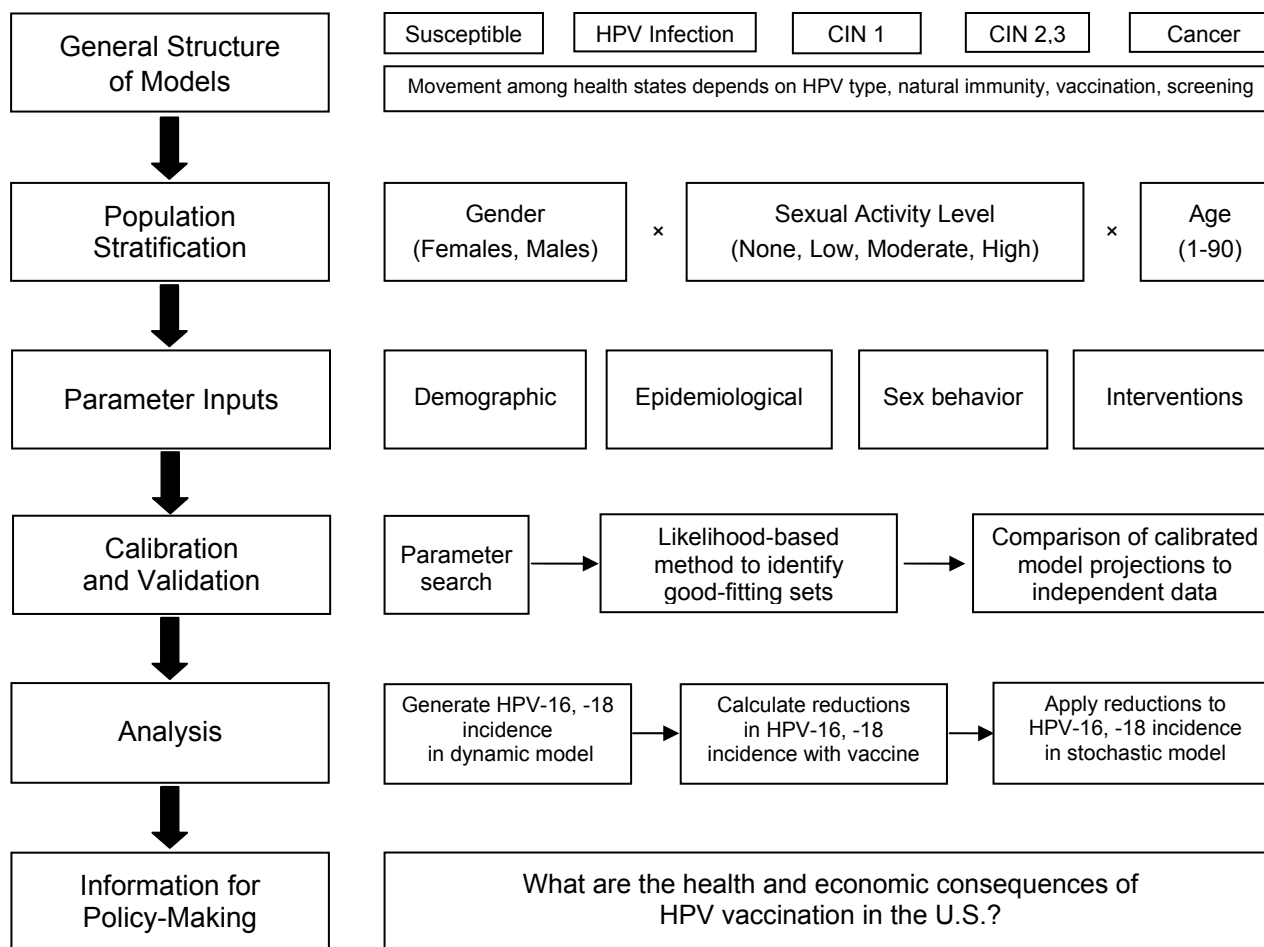
Supplement to: Kim JJ, Goldie SJ. Health and economic implications of HPV vaccination in the United States. N Engl J Med 2008;359:821-32.

**Health and Economic Implications of HPV Vaccination  
in the United States**

Jane J. Kim, Sue J. Goldie

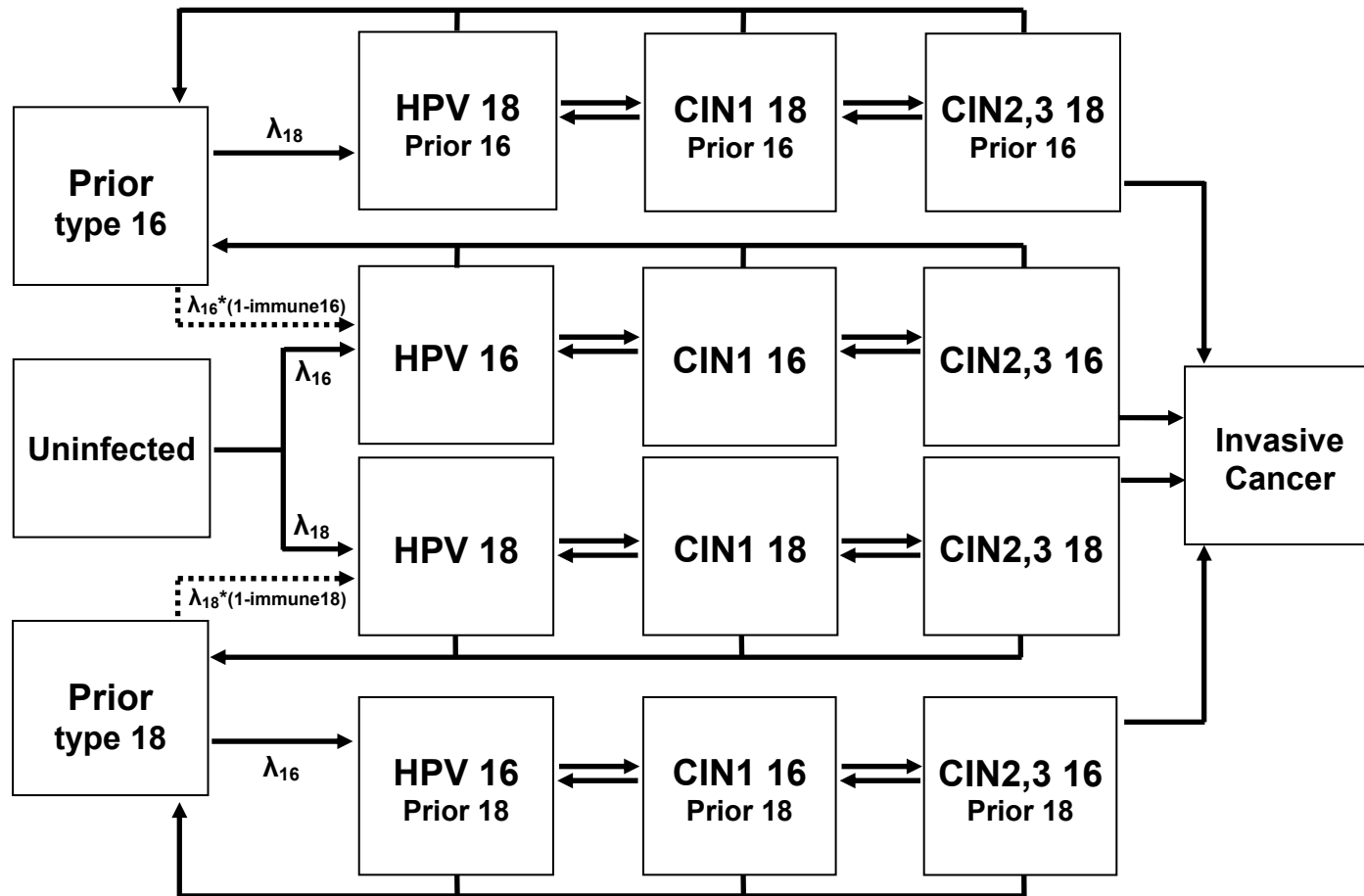
**SUPPLEMENTARY APPENDIX**

**Analytic overview of the study.** We used a flexible modeling approach that included a dynamic model, to simulate sexual transmission of HPV-16 and -18 infections between males and females, and a stochastic model, to simulate HPV-induced cervical carcinogenesis associated with all HPV types. Using population statistics, we stratified the population by gender and sexual activity level (in the dynamic model) and age (in both models). Using demographic statistics and data from epidemiological studies and cancer registries in the U.S., we parameterized the baseline model inputs. For uncertain parameters, the models were calibrated using a likelihood-based approach to fit to empirical data, primarily from the U.S. Using the calibrated dynamic model, we projected the reductions in HPV-16 and -18 incidence that would be expected over time with each HPV vaccination strategy. These estimates of reductions in HPV-16 and -18 incidence were then applied to the corresponding input parameters of HPV-16 and -18 incidence in the stochastic model, to account for the net impact of vaccination on cervical cancer outcomes associated with all HPV types. Long-term health and economic consequences were assessed for vaccination strategies that targeted preadolescent girls (i.e., 12 years of age) and included catch-up vaccination for older girls and women (i.e., to 18, 21, or 26 years of age).

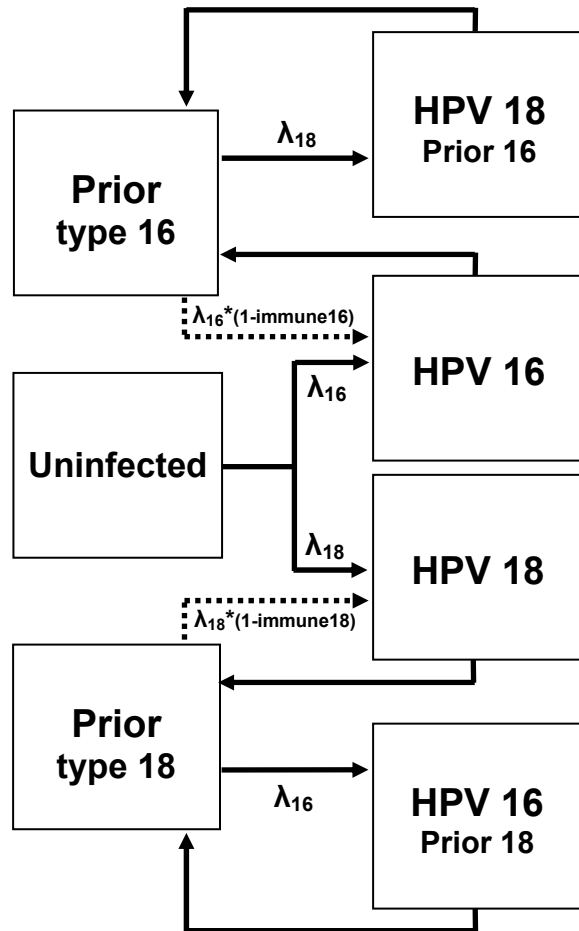


**Simplified schematic of dynamic model for females and males.** Females who are uninfected can acquire an HPV-16 or -18 infection (at an annual rate of  $\lambda_{16}$  or  $\lambda_{18}$ , respectively). Once infected, females can develop precancerous lesions (i.e., CIN1 and CIN2,3), and over time may develop invasive cervical cancer. Females who clear their infection or lesion develop a degree of natural immunity to that same HPV type (i.e., immune16 or immune18); future type-specific infections can be acquired at a reduced rate (e.g.,  $\lambda_{16}*(1-immune16)$ ). History of prior infection is tracked throughout the analysis. The model for males has a similar structure for HPV-16 and -18 infection only. Note: not all health states and transitions are shown (e.g., Prior 16+18, Dead). Once vaccination is introduced, covered females enter a corresponding vaccinated state; vaccine efficacy is modeled as protection against future type-specific infection among those without prior history of infection.

**FEMALES**



MALES



## BOUNDARY CONDITIONS

### Females

$$\begin{aligned} Sw_t(0,j) = \text{prop\_female} * \int_0^{\infty} \pi(i') * [ Sw_t(i', j) + lw16_t(i', j) + lw18_t(i', j) + L16_t(i', j) + L18_t(i', j) + H16_t(i', j) + H18_t(i', j) + CA16_t(i', j) + CA18_t(i', j) \\ + Histw16_t(i', j) + Histw18_t(i', j) + Histw1618_t(i', j) + Histw18\_I16_t(i', j) + Histw16\_I18_t(i', j) \\ + Histw18\_L16_t(i', j) + Histw16\_L18_t(i', j) + Histw18\_H16_t(i', j) + Histw16\_H18_t(i', j) + Vw_t(i', j)] di' \end{aligned}$$

### Males

$$\begin{aligned} Sm_t(0,j) = (1-\text{prop\_female}) * \int_0^{\infty} \pi(i') * [ Sw_t(i', j) + lw16_t(i', j) + lw18_t(i', j) + L16_t(i', j) + L18_t(i', j) + H16_t(i', j) + H18_t(i', j) + CA16_t(i', j) + CA18_t(i', j) \\ + Histw16_t(i', j) + Histw18_t(i', j) + Histw1618_t(i', j) + Histw18\_I16_t(i', j) + Histw16\_I18_t(i', j) \\ + Histw18\_L16_t(i', j) + Histw16\_L18_t(i', j) + Histw18\_H16_t(i', j) + Histw16\_H18_t(i', j) + Vw_t(i', j)] di' \end{aligned}$$

## STATE TRANSITION EQUATIONS

### Females

$$Sw_{t+1}(i,j) = Sw_t(i,j) + \text{prop\_female} * \pi(i) - [\lambda w16_t(i,j) + \lambda w18_t(i,j) + \text{vacc}(i) * \text{efficacy} + \mu w(i)] * Sw_t(i,j)$$

$$lw16_{t+1}(i,j) = lw16_t(i,j) + \lambda w16_t(i,j) * Sw_t(i,j) + \text{CIN1regr} * (1 - \text{CIN1clear}) * L16_t(i,j) + (1 - \text{imm\_degree16}) * \lambda w16_t(i,j) * Histw16_t(i,j) - [\text{HPVclear} + \text{HPVprog} + \text{vacc}(i) * \text{efficacy\_hx} + \mu w(i)] * lw16_t(i,j)$$

$$lw18_{t+1}(i,j) = lw18_t(i,j) + \lambda w18_t(i,j) * Sw_t(i,j) + \text{CIN1regr} * (1 - \text{CIN1clear}) * L18_t(i,j) + (1 - \text{imm\_degree18}) * \lambda w18_t(i,j) * Histw18_t(i,j) - [\text{HPVclear} + \text{HPVprog} + \text{vacc}(i) * \text{efficacy\_hx} + \mu w(i)] * lw18_t(i,j)$$

$$L16_{t+1}(i,j) = L16_t(i,j) + \text{HPVprog} * (\text{propCIN1}) * lw16_t(i,j) + \text{CIN23regr} * (1 - \text{CIN23clear}) * H16_t(i,j) - [\text{CIN1regr} + \text{CIN1prog} + \text{vacc}(i) * \text{efficacy\_hx} + \mu w(i)] * L16_t(i,j)$$

$$L18_{t+1}(i,j) = L18_t(i,j) + \text{HPVprog} * (\text{propCIN1}) * lw18_t(i,j) + \text{CIN23regr} * (1 - \text{CIN23clear}) * H18_t(i,j) - [\text{CIN1regr} + \text{CIN1prog} + \text{vacc}(i) * \text{efficacy\_hx} + \mu w(i)] * L18_t(i,j)$$

$$H16_{t+1}(i,j) = H16_t(i,j) + \text{HPVprog} * (1 - \text{propCIN1}) * lw16_t(i,j) + \text{CIN1prog} * L16_t(i,j) - [\text{CIN23regr} + \text{CIN23prog} + \text{vacc}(i) * \text{efficacy\_hx} + \mu w(i)] * H16_t(i,j)$$

$$H18_{t+1}(i,j) = H18_t(i,j) + \text{HPVprog} * (1 - \text{propCIN1}) * lw18_t(i,j) + \text{CIN1prog} * L18_t(i,j) - [\text{CIN23regr} + \text{CIN23prog} + \text{vacc}(i) * \text{efficacy\_hx} + \mu w(i)] * H18_t(i,j)$$

$$CA16_{t+1}(i,j) = CA16_t(i,j) + \text{CIN23prog} * [H16_t(i,j) + Histw18\_H16_t(i,j)] - [\mu w(i) + \mu CA] * CA16_t(i,j)$$

$$CA18_{t+1}(i,j) = CA18_{t,i,j} + CIN23prog*[H18_{t,i,j} + Histw16\_H18_{t,i,j}] - [\mu w(i) + \mu CA]*CA18_{t,i,j}$$

$$Histw16_{t+1}(i,j) = Histw16_{t,i,j} + HPVclear*lw16_{t,i,j} + CIN1 regr*CIN1clear*L16_{t,i,j} + CIN23 regr*CIN23clear*H16_{t,i,j} - [(1-imm\_degree16)*\lambda w16_{t,i,j} + \lambda w18_{t,i,j} + vacc(i)*efficacy\_hx + \mu w(i)]*Histw16_{t,i,j}$$

$$Histw18_{t+1}(i,j) = Histw18_{t,i,j} + HPVclear*lw18_{t,i,j} + CIN1 regr*CIN1clear*L18_{t,i,j} + CIN23 regr*CIN23clear*H18_{t,i,j} - [(1-imm\_degree18)*\lambda w18_{t,i,j} + \lambda w16_{t,i,j} + vacc(i)*efficacy\_hx + \mu w(i)]*Histw18_{t,i,j}$$

$$Histw1618_{t+1}(i,j) = Histw1618_{t,i,j} + HPVclear*[Histw18\_L16_{t,i,j} + Histw16\_L18_{t,i,j}] + CIN1 regr*CIN1clear*[Histw18\_L16 + Histw16\_L18] + CIN23 regr*CIN23clear*[Histw18\_H16 + Histw16\_H18] - [(1-imm\_degree16)*\lambda w16_{t,i,j} + (1-imm\_degree18)*\lambda w18_{t,i,j} + vacc(i)*efficacy\_hx + \mu w(i)]*Histw1618_{t,i,j}$$

$$Histw18\_L16_{t+1}(i,j) = Histw18\_L16_{t,i,j} + \lambda w16_{t,i,j}*Histw18_{t,i,j} + (1-imm\_degree16)*\lambda w16_{t,i,j}*Histw1618_{t,i,j} + CIN1 regr*(1-CIN1clear)*Histw18\_L16_{t,i,j} - [HPVprog + HPVclear + vacc(i)*efficacy\_hx + \mu w(i)]*Histw18\_L16_{t,i,j}$$

$$Histw16\_L18_{t+1}(i,j) = Histw16\_L18_{t,i,j} + \lambda w18_{t,i,j}*Histw16_{t,i,j} + (1-imm\_degree18)*\lambda w18_{t,i,j}*Histw1618_{t,i,j} + CIN1 regr*(1-CIN1clear)*Histw16\_L18_{t,i,j} - [HPVprog + HPVclear + vacc(i)*efficacy\_hx + \mu w(i)]*Histw16\_L18_{t,i,j}$$

$$Histw18\_L16_{t+1}(i,j) = Histw18\_L16_{t,i,j} + HPVprog*propCIN1*Histw18\_L16_{t,i,j} + CIN23 regr*(1-CIN23clear)*Histw18\_H16_{t,i,j} - [CIN1 regr + CIN1prog + vacc(i)*efficacy\_hx + \mu w(i)]*Histw18\_L16_{t,i,j}$$

$$Histw16\_L18_{t+1}(i,j) = Histw16\_L18_{t,i,j} + HPVprog*propCIN1*Histw16\_L18_{t,i,j} + CIN23 regr*(1-CIN23clear)*Histw16\_H18_{t,i,j} - [CIN1 regr + CIN1prog + vacc(i)*efficacy\_hx + \mu w(i)]*Histw16\_L18_{t,i,j}$$

$$Histw18\_H16_{t+1}(i,j) = Histw18\_H16_{t,i,j} + HPVprog*(1-propCIN1)*Histw18\_L16_{t,i,j} + CIN1prog*Histw18\_L16_{t,i,j} - [CIN23 regr + CIN23prog + vacc(i)*efficacy\_hx + \mu w(i)]*Histw18\_H16_{t,i,j}$$

$$Histw16\_H18_{t+1}(i,j) = Histw16\_H18_{t,i,j} + HPVprog*(1-propCIN1)*Histw16\_L18_{t,i,j} + CIN1prog*Histw16\_L18_{t,i,j} - [CIN23 regr + CIN23prog + vacc(i)*efficacy\_hx + \mu w(i)]*Histw16\_H18_{t,i,j}$$

$$Vw_{t+1}(i,j) = Vw_{t,i,j} + vacc(i)*efficacy*Sw_{t,i,j} + vacc(i)*efficacy\_hx*[lw16_{t+1}(i,j) + lw18_{t+1}(i,j) + L16_{t+1}(i,j) + L18_{t+1}(i,j) + H16_{t+1}(i,j) + H18_{t+1}(i,j) + Histw16_{t+1}(i,j) + Histw18_{t+1}(i,j) + Histw1618_{t+1}(i,j) + Histw18\_L16_{t+1}(i,j) + Histw16\_L18_{t+1}(i,j) + Histw18\_H16_{t+1}(i,j) + Histw16\_H18_{t+1}(i,j)] - \mu w(i)*Vw_{t,i,j}$$

### Males

$$Sm_{t+1}(i,j) = Sm_{t,i,j} + (1-prop\_female)*\pi(i) - [\lambda m16_{t,i,j} + \lambda m18_{t,i,j} + \mu m(i)]*Sm_{t,i,j}$$

$$Im16_{t+1}(i,j) = Im16_{t,i,j} + \lambda m16_{t,i,j}*Sm_{t,i,j} + (1-imm\_degree16)*\lambda m16_{t,i,j}*Histm16_{t,i,j} - [HPVclear + \mu m(i)]*Im16_{t,i,j}$$

$$Im18_{t+1}(i,j) = Im18_{t,i,j} + \lambda m18_{t,i,j}*Sm_{t,i,j} + (1-imm\_degree18)*\lambda m18_{t,i,j}*Histm18_{t,i,j} - [HPVclear + \mu m(i)]*Im18_{t,i,j}$$

$$Histm16_{t+1}(i,j) = Histm16_{t,i,j} + HPVclear*Im16_{t,i,j} - [(1-imm\_degree16)*\lambda m16_{t,i,j} + \lambda m18_{t,i,j} + \mu m(i)]*Histm16_{t,i,j}$$

$$\text{Hism18}_{t+1}(i,j) = \text{Hism18}_t(i,j) + \text{HPVclear} * \text{Im18}_t(i,j) - [(1 - \text{imm\_degree18}) * \lambda_{m18_t}(i,j) + \lambda_{m16_t}(i,j) + \mu_m(i)] * \text{Hism18}_t(i,j)$$

$$\text{Hism1618}_{t+1}(i,j) = \text{Hism1618}_t(i,j) + \text{HPVclear} * [\text{Hism18\_I16}_t(i,j) + \text{Hism16\_I18}_t(i,j)] - [(1 - \text{imm\_degree16}) * \lambda_{m16_t}(i,j) + (1 - \text{imm\_degree18}) * \lambda_{m18_t}(i,j) + \mu_m(i)] * \text{Hism1618}_t(i,j)$$

$$\text{Hism18\_I16}_{t+1}(i,j) = \text{Hism18\_I16}_t(i,j) + \lambda_{m16_t}(i,j) * \text{Hism18}_t(i,j) + (1 - \text{imm\_degree16}) * \lambda_{m16_t}(i,j) * \text{Hism1618}_t(i,j) - [\text{HPVclear} + \mu_m(i)] * \text{Hism18\_I16}_t(i,j)$$

$$\text{Hism16\_I18}_{t+1}(i,j) = \text{Hism16\_I18}_t(i,j) + \lambda_{m18_t}(i,j) * \text{Hism16}_t(i,j) + (1 - \text{imm\_degree18}) * \lambda_{m18_t}(i,j) * \text{Hism1618}_t(i,j) - [\text{HPVclear} + \mu_m(i)] * \text{Hism16\_I18}_t(i,j)$$

## FORCE OF INFECTION <sup>1</sup>

$$\lambda w16_t(i, j) = \sum_{k=1}^{90} \sum_{l=1}^4 kw(i, j) \cdot \rho w_t(i, j, k, l) \cdot \frac{\beta16 \cdot (\text{Im}16_t(k, l) + \text{Histm}18\_116_t(k, l))}{\text{Nm}_t(k, l)}$$

$$\lambda w18_t(i, j) = \sum_{k=1}^{90} \sum_{l=1}^4 kw(i, j) \cdot \rho w_t(i, j, k, l) \cdot \frac{\beta18 \cdot (\text{Im}18_t(k, l) + \text{Histm}16\_118_t(k, l))}{\text{Nm}_t(k, l)}$$

$$\lambda m16_t(i, j) = \sum_{k=1}^{90} \sum_{l=1}^4 km(i, j) \cdot \rho m_t(i, j, k, l) \cdot \frac{\beta16 \cdot (\text{Iw}16_t(k, l) + \text{L}16_t(k, l) + \text{H}16_t(k, l) + \text{Histw}18\_116_t(k, l) + \text{Histw}18\_116_t(k, l) + \text{Histw}18\_116_t(k, l))}{\text{Nw}_t(k, l)}$$

$$\lambda m18_t(i, j) = \sum_{k=1}^{90} \sum_{l=1}^4 km(i, j) \cdot \rho m_t(i, j, k, l) \cdot \frac{\beta18 \cdot (\text{Iw}18_t(k, l) + \text{L}18_t(k, l) + \text{H}18_t(k, l) + \text{Histw}16\_118_t(k, l) + \text{Histw}16\_118_t(k, l) + \text{Histw}16\_118_t(k, l))}{\text{Nw}_t(k, l)}$$

## SEXUAL MIXING MATRIX

We used a similar sexual mixing algorithm as described by Barnabas et al. (2006)<sup>1</sup>:

$$\rho w_t(i, j, k, l) = \left[ \begin{array}{c} \varepsilon_1 \cdot \frac{\sum_{l=1}^4 \text{Nm}_t(k, l) \cdot km(k, l)}{\sum_{k=1}^{90} \sum_{l=1}^4 \text{Nm}_t(k, l) \cdot km(k, l)} + (1 - \varepsilon_1) \cdot \delta(i, k) \\ \varepsilon_2 \cdot \frac{\text{Nm}_t(k, l) \cdot km(k, l)}{\sum_{l=1}^4 \text{Nm}_t(k, l) \cdot km(k, l)} + (1 - \varepsilon_2) \cdot \delta(j, l) \end{array} \right]$$

$$\rho m_t(i, j, k, l) = \left[ \begin{array}{c} \varepsilon_1 \cdot \frac{\sum_{l=1}^4 \text{Nw}_t(k, l) \cdot kw(k, l)}{\sum_{k=1}^{90} \sum_{l=1}^4 \text{Nw}_t(k, l) \cdot kw(k, l)} + (1 - \varepsilon_1) \cdot \delta(i, k) \\ \varepsilon_2 \cdot \frac{\text{Nw}_t(k, l) \cdot kw(k, l)}{\sum_{l=1}^4 \text{Nw}_t(k, l) \cdot kw(k, l)} + (1 - \varepsilon_2) \cdot \delta(j, l) \end{array} \right]$$

## DESCRIPTION OF MODEL STATE VARIABLES

<i>Females</i>	
$Sw_{t(i,j)}$	Susceptible women (age $i$ , sexual activity group $j$ ) with no infection and no history of infection at time $t$
$Iw16_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) infected with HPV-16 at time $t$
$Iw18_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) infected with HPV-18 at time $t$
$L16_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) with low-grade precancerous lesion (i.e., CIN 1) associated with HPV-16 at time $t$
$L18_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) with low-grade precancerous lesion (i.e., CIN 1) associated with HPV-18 at time $t$
$H16_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) with high-grade precancerous lesion (i.e., CIN 2,3) associated with HPV-16 at time $t$
$H18_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) with high-grade precancerous lesion (i.e., CIN 2,3) associated with HPV-18 at time $t$
$CA16_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) with invasive cancer associated with HPV-16 at time $t$
$CA18_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) with invasive cancer associated with HPV-18 at time $t$
$Histw16_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) with history of prior HPV-16 infection and clearance at time $t$
$Histw18_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) with history of prior HPV-18 infection and clearance at time $t$
$Histw1618_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) with history of prior HPV-16 and -18 infections and clearance at time $t$
$Histw18\_I16_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) with HPV-16 infection who have a history of prior HPV-18 infection at time $t$
$Histw16\_I18_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) with HPV-18 infection who have a history of prior HPV-16 infection at time $t$
$Histw18\_L16_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) with CIN1 associated with HPV-16 who have a history of prior HPV-18 infection at time $t$
$Histw16\_L18_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) with CIN1 associated with HPV-18 who have a history of prior HPV-16 infection at time $t$
$Histw18\_H16_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) with CIN2,3 associated with HPV-16 who have a history of prior HPV-18 infection at time $t$
$Histw16\_H18_{t(i,j)}$	Women (age $i$ , sexual activity group $j$ ) with CIN2,3 associated with HPV-18 who have a history of prior HPV-16 infection at time $t$
$Vw_{t(i,j)}$	Vaccinated women (age $i$ , sexual activity group $j$ ) at time $t$
$Nw_{t(i,j)}$	Total number of women (age $i$ , sexual activity group $j$ ) at time $t$
<i>Males</i>	
$Sm_{t(i,j)}$	Susceptible men (age $i$ , sexual activity group $j$ ) with no infection and no history of infection at time $t$
$Im16_{t(i,j)}$	Men (age $i$ , sexual activity group $j$ ) infected with HPV-16 at time $t$
$Im18_{t(i,j)}$	Men (age $i$ , sexual activity group $j$ ) infected with HPV-18 at time $t$
$Histm16_{t(i,j)}$	Men (age $i$ , sexual activity group $j$ ) with history of prior HPV-16 infection and clearance at time $t$
$Histm18_{t(i,j)}$	Men (age $i$ , sexual activity group $j$ ) with history of prior HPV-18 infection and clearance at time $t$
$Histm1618_{t(i,j)}$	Men (age $i$ , sexual activity group $j$ ) with history of prior HPV-16 and -18 infections and clearance at time $t$
$Histm18\_I16_{t(i,j)}$	Men (age $i$ , sexual activity group $j$ ) with HPV-16 infection who have a history of prior HPV-18 infection at time $t$
$Histm16\_I18_{t(i,j)}$	Men (age $i$ , sexual activity group $j$ ) with HPV-18 infection who have a history of prior HPV-16 infection at time $t$
$Nm_{t(i,j)}$	Total number of men (age $i$ , sexual activity group $j$ ) at time $t$

**DESCRIPTION AND VALUES OF MODEL PARAMETERS \***

Variable Name	Description	Values	Source
prop_female	proportion of females in the U.S. population at t=0	0.5091	2
$\pi(i)$	birth rate, by age i	Appendix Table	3
vacc(i)	proportion of the targeted population vaccinated at age i	years 1-5: 25% years 6-10: 75%	assumed
efficacy	degree of vaccine protection against future HPV-16 and -18 infections among those without prior history of type-specific infection	100%	4-8
efficacy_hx	degree of vaccine protection against future HPV-16 and -18 infections among those with prior history of type-specific infection	0%	4-8
$\mu_w(i)$	all-cause mortality rates for females in U.S., by age i	0.00010 – 0.12465 †	9
$\mu_m(i)$	all-cause mortality rates for males in U.S., by age i	0.00011 – 0.16206 †	9
$\mu_{CA}$	excess mortality rate for females with invasive cancer	0.0646	10
$\lambda_{w16_t(i,j)}$	force of HPV-16 infection among women (age i, sexual activity group j) at time t	calculated by model	
$\lambda_{w18_t(i,j)}$	force of HPV-18 infection among women (age i, sexual activity group j) at time t	calculated by model	
$\lambda_{m16_t(i,j)}$	force of HPV-16 infection among men (age i, sexual activity group j) at time t	calculated by model	
$\lambda_{m18_t(i,j)}$	force of HPV-18 infection among men (age i, sexual activity group j) at time t	calculated by model	
$k_w(i,j)$	number of new partners per year for women (age i, sexual activity group j)	Appendix Table	11
$k_m(i,j)$	number of new partners per year for men (age i, sexual activity group j)	Appendix Table	11
$\rho_w(i,j,k,l)$	mixing matrix for women, representing the probability that women of age i and sexual activity group j forms a partnership with men of age k and sexual activity group l	calculated by model	1
$\rho_m(i,j,k,l)$	mixing matrix for men, representing the probability that men of age i and sexual activity group j forms a partnership with women of age k and sexual activity group l	calculated by model	1
$\beta_{16}$	transmission probability of HPV-16 infection per infected-susceptible partnership	0.823 ‡	calibrated
$\beta_{18}$	transmission probability of HPV-18 infection per infected-susceptible partnership	0.691 ‡	calibrated
$\epsilon_1$	mixing coefficient by age (0=assortative; 1=random)	0.3	assumed
$\epsilon_2$	mixing coefficient by sexual activity group (0=assortative; 1=random)	0.3	assumed
$\delta(i,k)$	identity matrix for age	1 if i=k; 0 otherwise	
$\delta(j,l)$	identity matrix for sexual activity group	1 if j=l; 0 otherwise	
HPVprog	probability of progression from HPV to CIN1 or CIN2,3 §	0.0667	12-15
propCIN1	proportion of women who progress from HPV to CIN1 (versus CIN2,3)	0.90	assumed 1, 14
HPVclear	probability of HPV-16 and HPV-18 clearance	0.3438	calibrated 14, 16, 17

**DESCRIPTION OF MODEL PARAMETERS (CONT) \***

CIN1prog(i)	probability of progression from CIN1 to CIN2,3, by age i	0.0167 – 0.6000 †	18-21
CIN1regr	probability of regression from CIN1	0.2667	14, 15, 17
CIN1clear	proportion of women who regress from CIN1 and clear their HPV infection	0.70	assumed
CIN23prog(i)	probability of progression from CIN2,3 to invasive cancer, by age i	0.0020 – 0.0301 † ¶	calibrated 10, 14, 17
CIN23regr	probability of regression from CIN2,3	0.0583	14, 15, 17
CIN23clear	proportion of women who regress from CIN2,3 and clear their HPV infection	0.70	assumed
imm_degree16	degree of natural immunity following HPV-16 infection and clearance (lifelong)	0.7550 #	calibrated
imm_degree18	degree of natural immunity following HPV-18 infection and clearance (lifelong)	0.6976 #	calibrated

\* HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia. Probabilities are annual unless otherwise noted.

† Range represents age-specific probabilities.

‡ In the calibration process, baseline probability was allowed to vary from 0.1 to 1.0.

§ A proportion of females (10%) with HPV who progress to CIN 1 transition directly to CIN 2,3.

|| In the calibration process, a baseline probability of 0.2667 was allowed to vary by a factor of 0-2.

¶ In the calibration process, baseline probabilities of 0.002-0.030 (by age) were allowed to vary by a factor of 1-6.

# Natural immunity represents the degree of protection individuals face against future type-specific infection after first infection and clearance; the values for type-specific natural immunity were obtained from a separate calibration exercise using the stochastic model.

## U.S. DEMOGRAPHIC DATA

Age	Population Size (2000) <sup>2</sup>		Fertility Rate (2006) <sup>3</sup> (annual, per woman)
	Males	Females	
0-4	9,831,175	9,386,999	--
5-9	10,488,829	9,994,277	--
10-14	10,560,818	10,047,597	0.0006
15-19	10,412,689	9,837,270	0.0419
20-24	9,821,860	9,363,203	0.1059
25-29	9,785,399	9,531,418	0.1168
30-34	10,372,884	10,214,189	0.0977
35-39	11,304,995	11,343,359	0.0473
40-44	11,179,973	11,355,395	0.0094
45-49	9,959,477	10,271,081	0.0006
50-54	8,706,996	9,083,620	0.0006
55-59	6,553,207	7,005,944	--
60-64	5,165,703	5,699,027	--
65-69	4,402,844	5,131,111	--
70-74	3,904,321	4,945,625	--
75-79	3,051,227	4,374,151	--
80+	3,093,305	6,158,663	--

## PROPORTION OF FEMALES AND MALES IN EACH SEXUAL ACTIVITY GROUP BY AGE

Age (years)	Sexual Activity Group (Number of New Partners Per Year) <sup>11</sup>			
	None (0)	Low (1-2)	Moderate (3-4)	High (5+)
<b>FEMALES</b>				
8-12	0.990	0.010	0	0
13-14	0.940	0.060	0	0
15-17	0.502	0.331	0.070	0.097
18-19	0.171	0.506	0.136	0.188
20-24	0.087	0.656	0.126	0.132
25-29	0.025	0.803	0.094	0.077
30-34	0.018	0.858	0.056	0.068
35-39	0.010	0.865	0.061	0.064
40-49	0.013	0.886	0.034	0.067
<b>MALES</b>				
8-12	0.990	0.010	0	0
13-14	0.940	0.060	0	0
15-17	0.524	0.314	0.084	0.077
18-19	0.247	0.423	0.162	0.168
20-24	0.090	0.559	0.127	0.224
25-29	0.047	0.738	0.066	0.149
30-34	0.027	0.795	0.068	0.111
35-39	0.019	0.842	0.050	0.090
40-49	0.018	0.836	0.055	0.092

## DYNAMIC MODEL CALIBRATION APPROACH

Four uncertain natural history parameters were selected for calibration: (1) transmission probability of HPV-16 per infected-susceptible partnership, (2) transmission probability of HPV-18 per infected-susceptible partnership, (3) clearance of HPV-16 and -18 infection, and (4) progression of CIN 2,3 to invasive cancer. For the transmission probabilities of HPV-16 and -18, we searched across a range of prior probabilities from 0.10 to 1.0; for HPV clearance and CIN 2,3 progression, we identified a plausible range of values using data from the published literature.<sup>10, 14, 16, 17</sup> Because we used two distinct models for this analysis, we carefully examined the consistency of parameter values and assumptions between the two models. The most important of these included type-specific immunity following clearance of first infection; we first estimated these values in a separate calibration exercise using our stochastic model, and then held these values constant in both models.

More than 100,000 model simulations were run in the absence of any vaccination or screening intervention. For each simulation, one value for each of the four parameters was randomly selected from a uniform distribution over the identified plausible ranges, creating a unique natural history parameter set. Model outcomes using each parameter set were scored according to their simultaneous fit with calibration targets that were based primarily on data from epidemiological studies and cancer registries in the U.S. (see **Calibration Target Data Table** below).

We specified likelihood functions for all calibration targets, assuming that each followed an independent normal distribution. For each of the 100,000+ parameter sets, we computed a composite goodness-of-fit score by summing over the individual log likelihood measures of all targets. Using a likelihood-ratio test, we identified the parameter sets that were statistically indistinguishable from the best-fitting parameter set; 1,397 parameter sets were identified, and were therefore deemed “good-fitting”.

In order to proceed with the base case analysis, we selected a parameter set that represents the average values of all four calibrated parameters in the dynamic model, across all 1,397 “good-fitting” sets (see table below for comparison).

### CALIBRATED PARAMETER VALUES \*

Variable	Baseline Probability	Parameter Search Range	Mean values from good-fitting sets (n=1,397)	Selected set for base case
Transmission probability per infected-susceptible partnership				
– HPV-16	0.5	0.1 – 1.0	0.832	0.823
– HPV-18	0.5	0.1 – 1.0	0.685	0.691
HPV clearance (HPV-16 and -18) <sup>14, 16, 17</sup>	0.267	0 – 2 †	1.315	1.289
CIN 2,3 to invasive cancer (HPV-16 and -18) <sup>10, 14, 17</sup>	0.002 – 0.030 ‡	1 – 6 †	1.018	1.002

\* HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia. Baseline probabilities are annual probabilities.

† Values represent factors that were multiplied to the baseline probability.

‡ Range represents age-specific probabilities.

## DYNAMIC MODEL CALIBRATION TARGET DATA\*

Calibration Target	Mean (SD)	Mean (SD)
<b>Prevalence of HPV infection among women</b> <sup>22-24</sup>	<b>HPV-16 †</b>	<b>HPV-18 †</b>
– 14-19 years	0.0390 (0.0078)	0.0147 (0.0048)
– 20-24 years	0.0759 (0.0198)	0.0295 (0.0121)
– 25-29 years	0.0487 (0.0165)	0.0211 (0.0101)
– 30-39 years	0.0471 (0.0120)	0.0201 (0.0077)
– 40-49 years	0.0415 (0.0114)	0.0173 (0.0071)
– 50-59 years	0.0336 (0.0114)	0.0146 (0.0069)
<b>Incidence rate of invasive cancer (per 100,000)</b> <sup>23, 25-27</sup>	<b>HPV-16 and -18 †</b>	
– 20-24 years	2.0 (1.0)	
– 25-29 years	10.4 (4.2)	
– 30-34 years	22.2 (6.0)	
– 35-39 years	28.1 (6.3)	
– 40-44 years	34.7 (6.2)	
– 45-49 years	35.6 (6.3)	
– 50-54 years	39.2 (7.6)	
– 55-59 years	41.9 (6.0)	
– 60-64 years	47.1 (8.7)	
– 65-69 years	51.2 (10.9)	
– 70-74 years	50.4 (12.0)	
– 75-79 years	48.6 (15.0)	
<b>Prevalence of HPV infection among men</b> <sup>28</sup>	<b>HPV-16 and -18</b>	
– 25-29 years	0.1000 (0.0255)	
– 30-34 years	0.0500 (0.0255)	
– 35-39 years	0.0250 (0.0128)	
– 40-44 years	0.0550 (0.0179)	
– 45-49 years	0.0450 (0.0179)	
– 50-54 years	0.0300 (0.0153)	
– 55-59 years	0.0375 (0.0140)	
– 60-64 years	0.0275 (0.0140)	

\* SD, standard deviation; HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia. All target data were assumed to follow normal distributions.

† To establish calibration targets of HPV prevalence and cervical cancer incidence associated with HPV types 16 and 18, we utilized data on type distribution of HPV-16 and -18 infections among U.S. women with no lesions<sup>23, 24</sup> and among U.S. women with invasive cervical cancer<sup>23, 25, 26</sup> and applied these proportions to HPV prevalence and cervical cancer incidence associated with all HPV types.<sup>22, 27</sup>

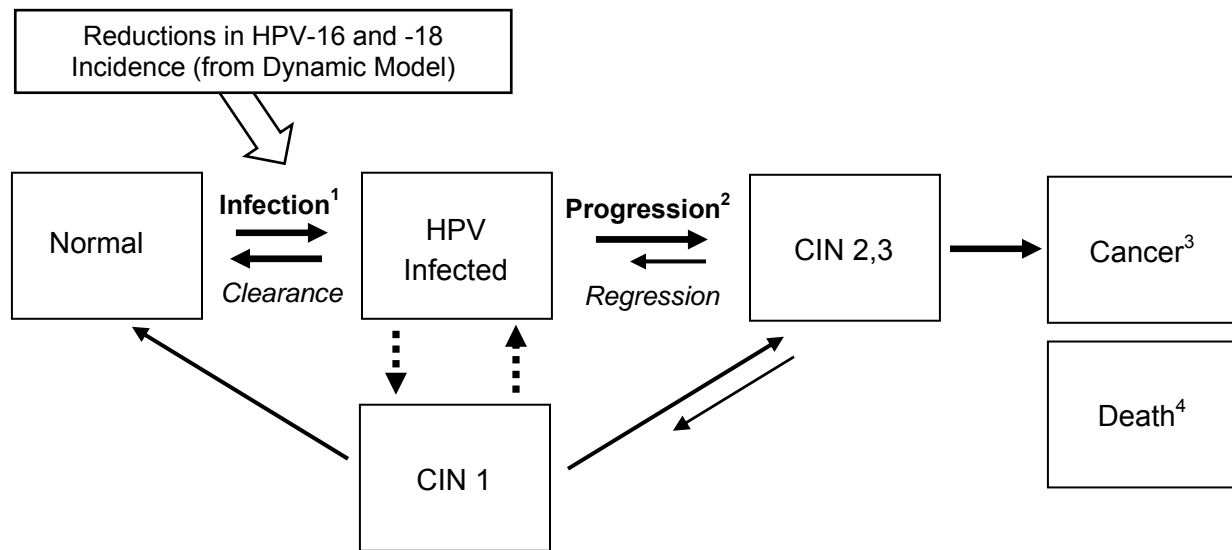
## LINKAGE OF DYNAMIC MODEL TO STOCHASTIC MODEL

We utilized two distinct mathematical models in a “hybrid” approach.<sup>29</sup> The dynamic model was run under various scenarios of vaccination over time (i.e., no vaccination, targeted pre-adolescent vaccination, and catch-up vaccination), and age-specific incidence for HPV-16 and -18 infections were generated each year using the force of infection ( $\lambda$ ) equations above.

We projected the reductions in HPV-16 and -18 incidences over the lifetimes of each sexually-active birth cohort over the first 10 years of the vaccination program, compared to no vaccination, regardless of whether or not they received the vaccine (in order to capture herd immunity in unvaccinated individuals; see Vaccine Analysis section below for more details). Reductions in age-specific HPV-16 and -18 incidence calculated from the dynamic model were then applied directly to the age-specific HPV-16 and -18 incidence inputs of the stochastic model (see simplified model schematic of stochastic model and linkage in the **Figure** below).

Details of the stochastic model structure, assumptions, and calibration are documented elsewhere.<sup>30</sup> Briefly, the stochastic model was calibrated using a similar likelihood-based approach and has a similar structure to the dynamic model, but offers the following key features: (1) only females are represented; (2) other HPV types are included, categorized as other (non-16,-18) high-risk types and low-risk types; (3) HPV incidence is a function of age and individual-level characteristics, but does not explicitly change over time in response to sexual activity and population prevalence; (4) it is an individual-based model, which reflects detailed heterogeneities among females, such as history of screening and/or treatment, and keeps track of individual-level expenditures; (5) it is stochastic, thereby able to capture variability as well as uncertainty; and (6) analyses can be run with a single birth cohort or multiple birth cohorts.<sup>30,31</sup>

Equations for the dynamic model were written and solved in Matlab; equations for the stochastic model were written and solved in C++.



<sup>1</sup> Incidence of infection depends on age, HPV type, prior infection, and type-specific immunity.

<sup>2</sup> Progression of HPV infection and CIN 1 depends on age and HPV type.

<sup>3</sup> Cancer states stratified by stage (i.e., local, regional, distant) and detection status (i.e., undetected, symptom-detected, screen-detected).

<sup>4</sup> Death can occur from all-cause mortality from every health state and excess cancer-specific mortality from cancer states.

## STOCHASTIC MODEL CALIBRATION

Parameter calibration of the stochastic model followed a similar approach as for the dynamic model, except for the following features: (1) we varied all natural history input parameters simultaneously; (2) the calibration targets were associated with all HPV types, including other high-risk and low-risk types; and (3) we searched over 1 million natural history parameter sets and selected the best-fitting set.

### CALIBRATED PARAMETER VALUES FOR BEST-FITTING SET\*

Variable	Baseline Values †	Parameter Search Range ‡	Best-Fitting Parameter Set
HPV incidence <sup>14, 17, 32-35</sup>			
HPV-16	0.0001 – 0.0100	0.1 – 8.0	4.747
HPV-18	0.0001 – 0.0100	0.1 – 8.0	1.760
HPV other high-risk	0.0001 – 0.0100	0.1 – 8.0	4.563
HPV low-risk	0.0001 – 0.0100	0.1 – 8.0	6.844
Progression of HPV incidence to CIN 1 <sup>12-15, 17, 36</sup>			
HPV-16	0.0047 – 0.0085	0.1 – 6.0	3.738
HPV-18	0.0047 – 0.0085	0.1 – 6.0	1.136
HPV other high-risk	0.0047 – 0.0085	0.1 – 6.0	2.745
HPV low-risk	0.0046 – 0.0054	0.1 – 6.0	0.398
Proportion of women with HPV who transition directly to CIN 2,3			
HPV-16	0.10	0.1 – 1.0	0.619
HPV-18	0	0 – 0.10	0.007
HPV other high-risk	0	0 – 0.10	0.055
HPV low-risk	0	0 – 0.10	0.028
Progression of CIN 1 to CIN 2,3 <sup>18-21, 37, 38</sup>			
HPV-16	0.0001 – 0.0039	0.1 – 6.0	1.927
HPV-18	0.0001 – 0.0039	0.1 – 6.0	4.552
HPV other high-risk	0.0001 – 0.0039	0.1 – 6.0	2.645
HPV low-risk	0.00001 – 0.0008	0.1 – 6.0	0.421
Progression of CIN 2,3 to invasive cancer <sup>10, 14, 17</sup>			
HPV-16	0.00001 – 0.0060	0.5 – 6.0	4.808
HPV-18	0.00001 – 0.0060	0.5 – 6.0	2.973
HPV other high-risk	0.00001 – 0.0060	0.5 – 4.0	1.719
HPV clearance <sup>14, 16, 17</sup>			
HPV-16	0.0305	0.5 – 8.0	6.732
HPV-18	0.0305	0.5 – 8.0	7.959
HPV other high-risk	0.0305	0.5 – 8.0	7.731
HPV low-risk	0.0305	0.5 – 8.0	4.057

### CALIBRATED PARAMETER VALUES FOR BEST-FITTING SET (CONT)\*

Variable	Baseline Values †	Parameter Search Range ‡	Best-Fitting Parameter Set
CIN 1 regression <sup>14, 15, 17 37</sup> §			
HPV-16	0.0305	0.5 – 6.0	3.412
HPV-18	0.0305	0.5 – 6.0	4.234
HPV other high-risk	0.0305	0.5 – 6.0	2.764
HPV low-risk	0.0305	0.5 – 6.0	3.055
CIN 2,3 regression <sup>14, 15, 17 37</sup>			
HPV-16	0.0014 – 0.0065	0.5 – 6.0	5.668
HPV-18	0.0014 – 0.0065	0.5 – 6.0	5.932
HPV other high-risk	0.0014 – 0.0065	0.5 – 6.0	4.868
HPV low-risk	0.0014 – 0.0065	0.5 – 6.0	2.560
Probability that a woman will develop a natural immune response after first HPV infection and clearance			
Any high-risk type	1.0	0.95 – 1.0	0.998
Reduction in HPV incidence after same type infection and clearance, conditional on immune response <sup>39</sup>			
HPV-16	1.0	0.4 – 1.0	0.755
HPV-18	1.0	0.4 – 1.0	0.698
HPV other high-risk	1.0	0 – 0.5	0.334
Progression of invasive cancer stages <sup>10, 14, 17</sup> ¶			
Local to regional	0.020	na	na
Regional to distant	0.025	na	na
5-year cervical cancer survival <sup>10</sup> ¶			
Local	0.92	na	na
Regional	0.56	na	na
Distant	0.17	na	na
Probability of symptom detection (annual) <sup>10</sup> ¶			
Local	0.19	na	na
Regional	0.60	na	na
Distant	0.90	na	na

\* HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia. Baseline probabilities are monthly probabilities unless otherwise noted.

† Values of parameters prior to calibration; ranges represent age-specific probabilities.

‡ Values represent factors that were multiplied to the baseline probability.

§ 70% of women with CIN 1 regress to Normal, 30% to HPV.

|| 70% of women with CIN 2,3 regress to Normal, 15% to HPV, 15% to CIN 1.

¶ These model parameters were not included in the model calibration process.

## STOCHASTIC MODEL CALIBRATION TARGET DATA\*

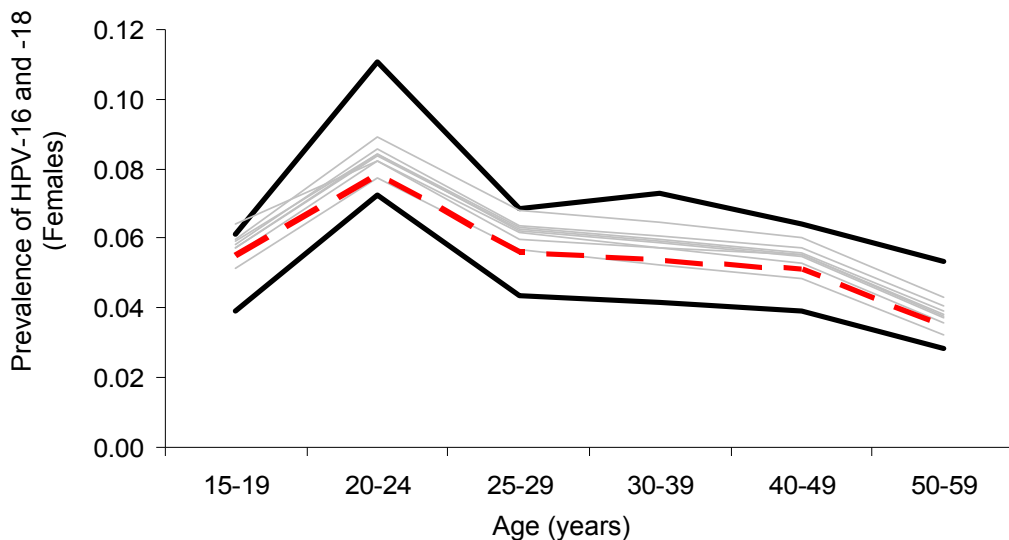
Calibration Target	Mean (SD)	Mean (SD)
<b>Prevalence of HPV infection among women</b> <sup>22</sup>	<b>Low-risk HPV</b>	<b>High-risk HPV</b>
– 14-19 years	0.145 (0.015)	0.188 (0.027)
– 20-24 years	0.325 (0.054)	0.295 (0.041)
– 25-29 years	0.223 (0.040)	0.150 (0.036)
– 30-39 years	0.200 (0.038)	0.179 (0.026)
– 40-49 years	0.153 (0.019)	0.149 (0.013)
– 50-59 years	0.175 (0.038)	0.078 (0.011)
<b>HPV type distribution</b> <sup>23-26, 40</sup>		
<i>Among women with CIN 1</i>		
HPV-16 and -18	0.304 (0.051)	
HPV other high-risk	0.491 (0.051)	
<i>Among women with CIN 2,3</i>		
HPV-16	0.346 (0.051)	
HPV-18	0.090 (0.046)	
HPV other high-risk	0.510 (0.051)	
<i>Among women with invasive cancer</i>		
HPV-16	0.551 (0.051)	
HPV-18	0.220 (0.051)	
<b>Incidence rate of invasive cancer (per 100,000)</b> <sup>27</sup>	<b>All HPV types</b>	
– 20-24 years	2.6 (1.4)	
– 25-29 years	13.5 (5.4)	
– 30-34 years	28.9 (7.8)	
– 35-39 years	36.4 (8.1)	
– 40-44 years	45.1 (8.1)	
– 45-49 years	46.1 (8.2)	
– 50-54 years	50.9 (9.9)	
– 55-59 years	54.4 (7.8)	
– 60-64 years	61.2 (11.3)	
– 65-69 years	66.4 (14.2)	
– 70-74 years	65.4 (15.5)	
– 75-79 years	63.1 (19.4)	

\* SD, standard deviation; HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia, grade 1 (CIN 1) or grade 2,3 (CIN 2,3). All target data were assumed to follow normal distributions.

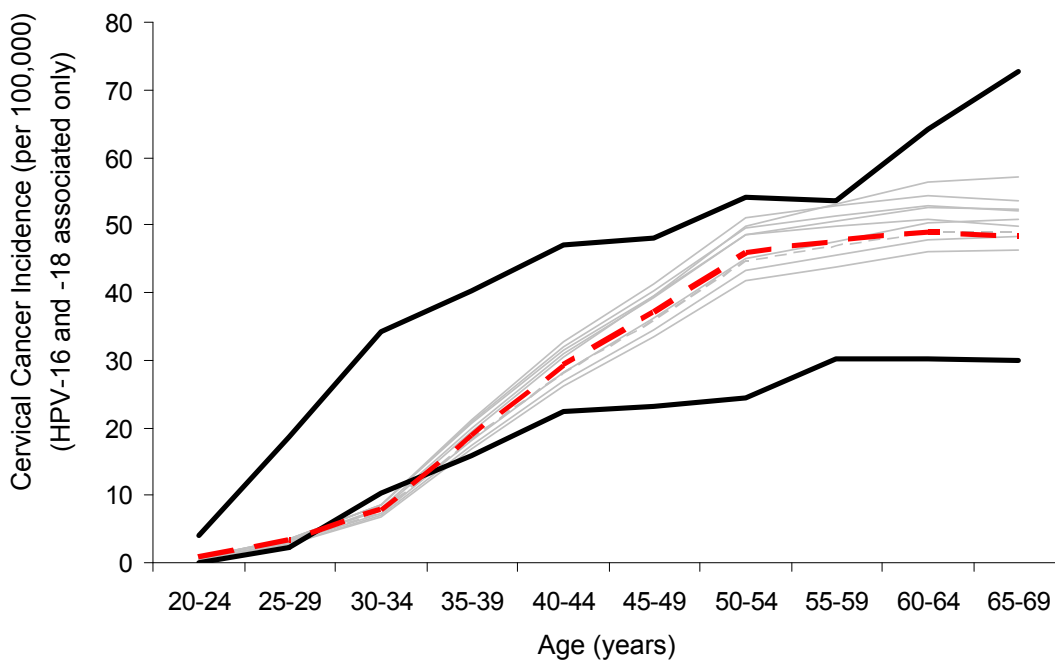
**MODEL CALIBRATION OUTPUT FROM A SAMPLE OF GOOD-FITTING SETS, COMPARED WITH EMPIRICAL DATA**

Red dotted lines represent model output for selected good-fitting set; gray lines represent model output for a sample of nine good-fitting sets. Black lines depict the 95% confidence interval of the empirical data at each age group.<sup>22-28</sup> “HRo” denotes other (non-16,-18) high-risk HPV types.

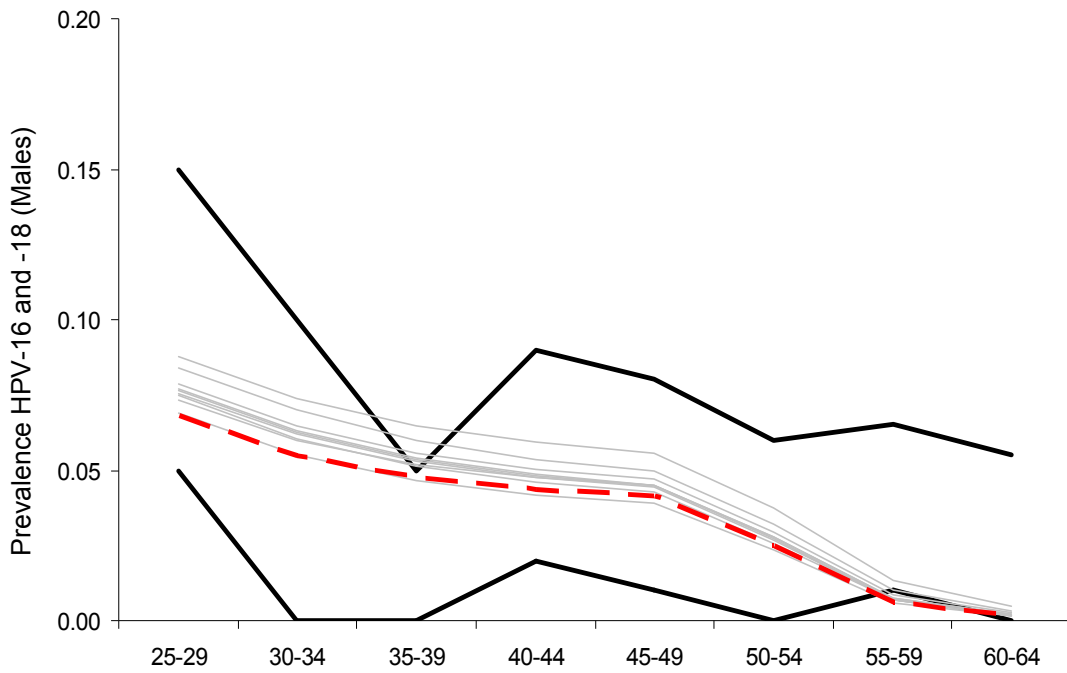
**A. Age-specific prevalence of HPV-16 and -18 among females from the dynamic model**



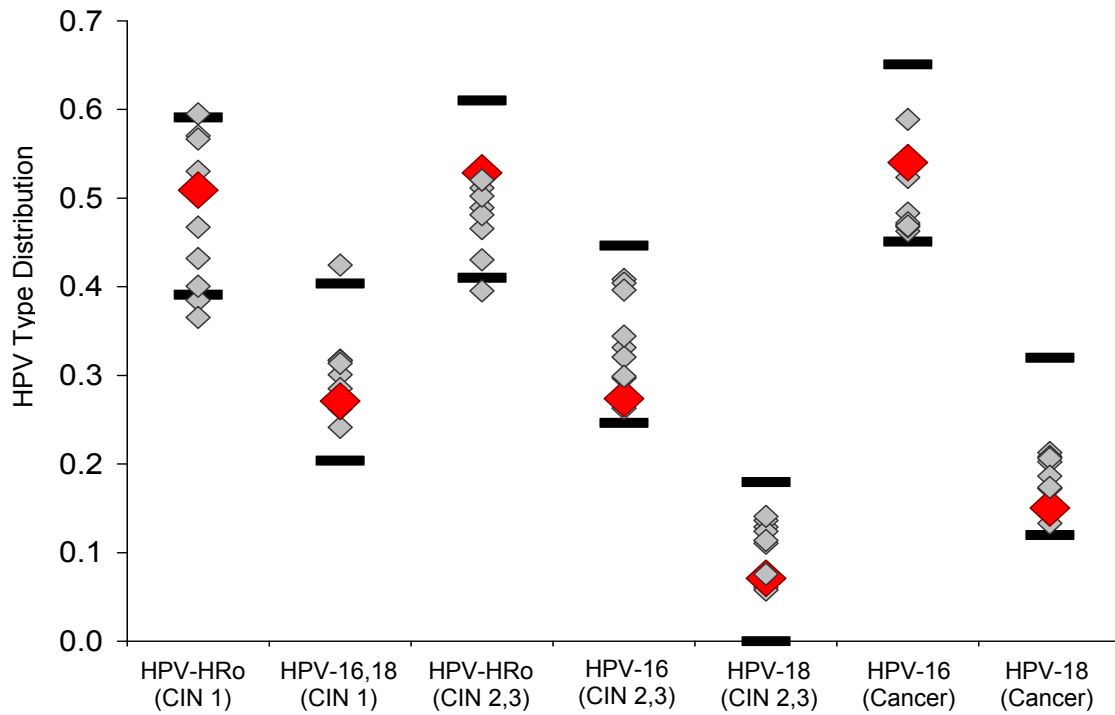
**B. Annual incidence of HPV-16 and -18 associated cervical cancer from the dynamic model**



**C. Age-specific prevalence of HPV-16 and -18 among males from the dynamic model**



**D. HPV type distribution among females with CIN and invasive cancer from the stochastic model**



## ESTIMATION OF NON-CERVICAL CANCER OUTCOMES

We used an incidence-based method to estimate the impact on HPV-6,-11 genital warts, and the possible impacts on HPV-6,-11 JORRP, by the quadrivalent vaccine, as well as other HPV-16,-18 cancers by both the bivalent and quadrivalent vaccines. The data required for these calculations included annual incidence of disease (age-specific when possible), proportion of cases attributable to vaccine-targeted HPV types, average cost per case, excess mortality rates (for cancer cases only), and health state utilities for each condition (see **Table 1** in main manuscript). All disease-specific utilities were multiplied to baseline age-specific utilities to estimate overall utility.<sup>41</sup> For the HPV-16,-18 associated non-cervical cancers, the dynamic model was used to estimate both direct and indirect (i.e., herd immunity) benefits from vaccination; for HPV-6,-11 warts and JORRP, vaccination is assumed to reduce only the proportion of cases attributable to vaccine-targeted types. Because of the greater uncertainty about vaccine effects on other cancers and JORRP, we varied efficacy on these conditions from 50% to 100% in sensitivity analysis. We also varied the proportion of warts cases attributable to HPV-6,-11. These incidence models were run both without and with the vaccination strategies to generate estimates of quality-adjusted life years gained and costs averted with each vaccination strategy. Both costs and quality-adjusted life years were discounted at a rate of 3% per year.

### Genital Warts

Age-specific annual incidence of genital warts was based on data from a study of over 3 million members of a private health insurance plan.<sup>42</sup> Based on the same data,<sup>42</sup> duration of genital warts was assumed to be, on average, three months. Health state utility was 0.91 during the episode of warts.<sup>43</sup> Proportion of genital warts cases attributable to HPV-6 or -11 was assumed to be 100%.<sup>44</sup> Cost of treating an episode of warts was, on average, \$430 (2006 U.S. dollars), reflecting direct medical costs associated with physician office visits for diagnosis and treatment, as well as pharmacy costs for medications and analgesics.<sup>45</sup> Embedded in the cost was an assumption that 25% of cases cured spontaneously.

### Juvenile Onset Recurrent Respiratory Papillomatosis (JORRP)

For JORRP, we counted cases and costs averted as a benefit of vaccinated women whose future offspring would face a reduced risk of JORRP. We utilized age-specific birth rates per woman, and applied an annual incidence rate of JORRP per live child. Birth rates from 2006 were obtained from the U.S. National Vital Statistics Reports,<sup>3</sup> and annual incidence of JORRP was estimated from a survey of otolaryngologists in the U.S.<sup>46</sup> Proportion of JORRP cases attributable to HPV-6 or -11 was assumed to be 100%.<sup>44</sup> Health state utility was assumed to be 0.69.<sup>47</sup> Cost per case of JORRP was, on average, \$62,010 (2006 U.S. dollars), reflecting direct medical costs associated with surgery, follow-up physician visits, and tracheotomy.<sup>45</sup>

### Other Cancers

Data on age-specific incidence and overall 5-year survival for vulva, vaginal, anal, mouth, and oropharynx cancers were obtained from the U.S. SEER Cancer registry (1975-2001).<sup>10</sup> Proportion of cases for each cancer attributable to HPV-16,-18 were reported in a 2006 monograph focused on burden of all HPV types worldwide.<sup>48</sup> Health state utility for all cancers was assumed to be, on average, 0.68 over the remaining lifetime, to reflect a weighted average of stage-specific utilities and stage distribution of disease.<sup>49</sup> Cost per case included diagnosis (e.g., biopsy), initial treatment (e.g., surgery or radiation), surveillance, management of metastatic disease, and terminal care.<sup>45</sup>

## SUMMARY COMPARISON OF MODEL FEATURES

	Dynamic Model	Stochastic Model	Incidence Models*
<b>HPV types included</b>	<ul style="list-style-type: none"> <li>▪ HPV-16</li> <li>▪ HPV-18</li> </ul>	<ul style="list-style-type: none"> <li>▪ HPV-16</li> <li>▪ HPV-18</li> <li>▪ Other High-Risk HPV</li> <li>▪ Low-Risk HPV</li> </ul>	<ul style="list-style-type: none"> <li>▪ HPV-16,-18</li> <li>▪ HPV-6,-11</li> </ul>
<b>Health conditions</b>	<ul style="list-style-type: none"> <li>▪ HPV-16 and -18 incidence</li> </ul>	<ul style="list-style-type: none"> <li>▪ Cervical cancer associated with all HPV types</li> </ul>	<ul style="list-style-type: none"> <li>▪ Genital warts associated with HPV-6,-11</li> <li>▪ JORRP associated with HPV-6,-11</li> <li>▪ Non-cervical cancers associated with HPV-16,-18</li> </ul>
<b>Important outcomes with each strategy</b>	<ul style="list-style-type: none"> <li>▪ Age-specific reductions in HPV-16 and HPV-18 incidences of different birth cohorts</li> </ul>	<ul style="list-style-type: none"> <li>▪ Reductions in lifetime risk of cervical cancer</li> <li>▪ Discounted quality-adjusted life expectancy gained</li> <li>▪ Discounted total costs gained or averted</li> </ul>	<ul style="list-style-type: none"> <li>▪ Discounted quality-adjusted life expectancy gained</li> <li>▪ Discounted total costs averted</li> </ul>

\* Separate incidence models were developed for each of the non-cervical cancer health conditions.

## A QUALITATIVE DESCRIPTION OF PROJECTED INFLUENCE OF INCLUDING DIFFERENT DISEASE OUTCOMES ON THE COST-EFFECTIVENESS RATIO

	Incidence without any intervention	Existing preventive intervention?	Incidence in setting of status quo intervention	Efficacy of the HPV vaccine
Cervical cancer	Low	Yes (screening)	Very low	High
Genital warts	High	No	unchanged	High
JORRP	Very low	No	unchanged	Uncertain
Other HPV cancers	Very low	No	unchanged	Uncertain

## VACCINE ANALYSIS

We evaluated all strategies over the first 10 years of the vaccination program by simulating their impact over the lifetimes of all birth cohorts that are sexually active throughout those 10 years. For example, at program year 1 ( $t=1$ ), the vaccine is introduced to girls who are 12 years old at that time. Even though a strategy without catch-up does not include vaccination of girls who are 13 years old at  $t=1$ , we model the 13-year-old cohort because they may reap downstream indirect benefits from herd immunity; same for girls who are older in that same year. At program year 2 ( $t=2$ ), a new cohort of 12-year-old girls is vaccinated, and we include their life histories in the analysis. We include incoming 12-year-old girls through program year 10 ( $t=10$ ). Essentially, for each strategy, we evaluate 38 birth cohorts in vaccine year 1 (girls who are ages 12 through 49, since we assume acquisition of new partners ceases after age 49), and then the 9 additional cohorts of 12-year-old girls that are vaccinated each year until program year 10. We repeat this analysis for each strategy because the level of herd immunity benefits (as well as direct benefits) for the included birth cohorts will differ by catch-up strategy.

Strategies include HPV vaccination of 12-year-old girls, and catch-up vaccination over a five-year period for females from age 13 up to 18, 21, or 26. We assume that approximately 75% of the target population is covered within the first five years of the vaccination program, at a coverage rate of 25% per year. For example, without a catch-up program, 25% of the initial 12-year-old birth cohort at vaccination program year 1 are covered with no opportunities for vaccination in future years. In strategies with a catch-up program, however, an additional 25% of the initial 12-year-old cohort who were not vaccinated in the first year have another opportunity to be vaccinated in the second year of the program, when they are 13 years old; such opportunities continue through program year 5. The number of vaccination opportunities depends on the specific catch-up strategy; for example, a 16-year-old in the first year of the program will have only three chances of being vaccinated in a catch-up program up to age 18, since she will age beyond 18 in program year 4.

## SCREENING ASSUMPTIONS

All strategies include routine cervical cancer screening with conventional or liquid-based cytology, beginning at an average age of 20, based on U.S. guidelines that recommend screening start three years after sexual debut.<sup>11, 50</sup> Women with cytology results of atypical squamous cells of undetermined significance (ASCUS) are managed using triage HPV DNA testing; those who test positive for high-risk types of HPV receive colposcopy and/or biopsy, while those who test negative return to routine screening. Women with positive cytology results are referred for colposcopy and/or biopsy; those with histologically confirmed CIN 1 are not treated but monitored every 6-12 months until they have three negative screening tests. Women with a positive diagnosis for CIN 2,3 or invasive cancer are treated according to standard guidelines.<sup>51</sup> Women with any confirmed abnormality, even if treated successfully for CIN, are screened annually until there are three consecutive negative results.

Based on cervical cancer screening patterns reported for U.S. women,<sup>52</sup> we assume that 53% of women are screened annually, 17% are screened every two years, 11% are screened every three years, 14% are screened every five years, and 5% are never screened. According to the 2005 NHIS survey,<sup>52</sup> 9% of women had not been screened at all in the past six years; we split that group into 5% who are never screened in their lifetime, and assume the remaining 4% are screened every five years. The survey also indicated that 9% of women were screened less than triennially, and we assume that all of those women are screened every five years.

## CERVICAL CANCER SCREENING AND COST PARAMETERS \*

Variable	Baseline values
Frequency of screening (percent of population) <sup>52</sup>	1-year (53%) 2-year (17%) 3-year (11%) 5-year (14%) Never (5%)
Test characteristics (%)	
Cytology <sup>53-55</sup> †	
Sensitivity (CIN 1/CIN 2,3)	70/80
Specificity	95
HPV DNA test <sup>55, 56</sup> ‡	
Sensitivity (CIN 1/CIN 2,3)	83/93
Specificity	93
Costs (2006 US dollars) §	
HPV vaccine (per dose) <sup>57-60</sup>	
Vaccine and wastage	134
Supplies and administration	9
Patient time and transport	24
Screening test <sup>61-65</sup>	
Cytology	32
HPV DNA test (Hybrid Capture II)	49
Office visit	27
Patient time and transport	26
Diagnostic follow-up <sup>61-64</sup>	
Colposcopy	364
Biopsy	53
Office visit	61
Patient time and transport	51
Treatment for CIN 2,3 <sup>62</sup> ¶	3,438
Treatment for cervical cancer <sup>62</sup> ¶	
Local invasive cancer	26,540
Regional invasive cancer	28,430
Distant invasive cancer	45,540

\* CIN, cervical intraepithelial neoplasia, grade 1 (CIN 1) or grade 2,3 (CIN 2,3); HPV, human papillomavirus.

† 50% of women are assumed to receive conventional cytology, and 50% liquid-based cytology. Sensitivity for detecting CIN 2,3 was calculated as the weighted average of values from two recent studies reporting conventional and liquid-based cytology sensitivities using an ASCUS+ threshold. <sup>54, 55</sup>

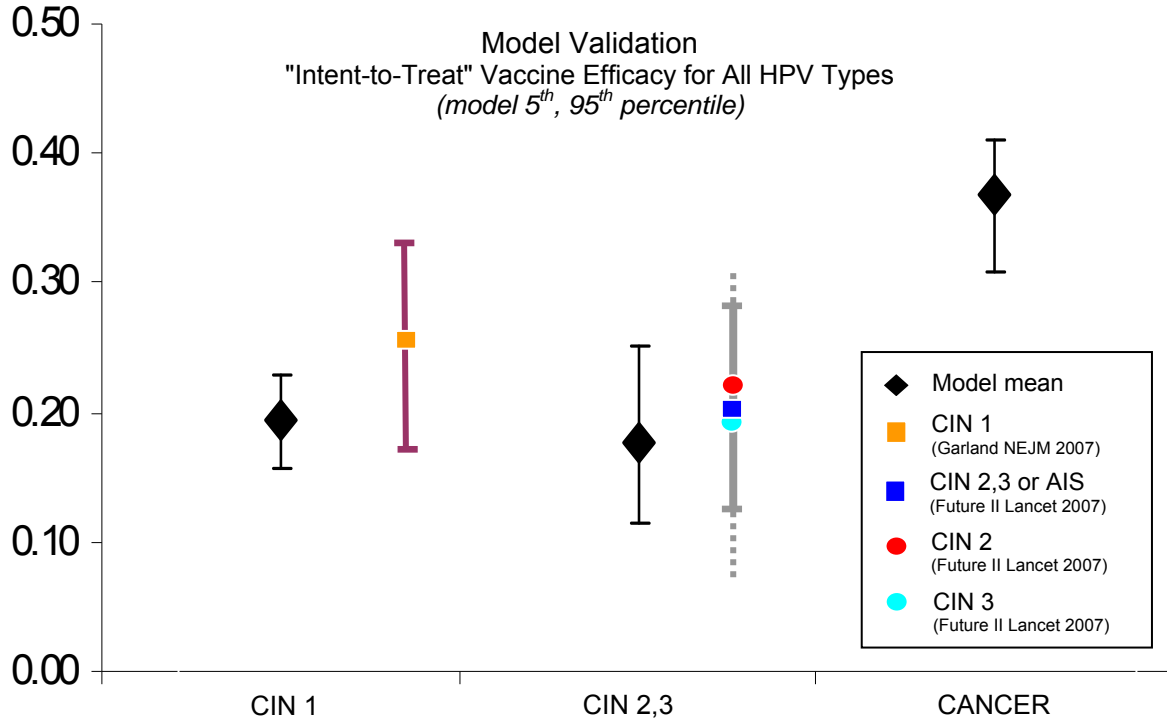
‡ HPV DNA testing is assumed to be 100% sensitive (specific) in detecting the presence (absence) of high-risk HPV types. When this assumption is made, the model generates an implied clinical sensitivity for detecting CIN 1 and CIN 2,3 of 83.0% and 93.0%, respectively, and specificity of 93.0%.

§ Costs were inflation-adjusted to constant 2006 U.S. dollars (USD) using the medical component of the Consumer Price Index. <sup>66</sup>

|| Vaccination assumes three doses; cost per-vaccinated individual is \$500.

¶ Treatment costs were inclusive of cost of procedures, office visit, and woman's time and transport.

## MODEL VALIDATION AGAINST VACCINE CLINICAL TRIAL RESULTS



## ADDITIONAL RESULTS

### EFFECT OF GENITAL WARTS CASES ATTRIBUTABLE TO HPV-6,-11 \*

Strategy †	100% (Base Case)	75%
Screening alone	--	--
Vaccination (age 12)	34,900	36,900
Vaccination (age 12) + catch-up (13-18)	81,000	84,600
Vaccination (age 12) + catch-up (13-21)	101,300	105,500
Vaccination (age 12) + catch-up (13-26)	133,600	138,000

\* Values represent incremental cost-effectiveness ratios (additional cost divided by additional health benefit compared to the next-less-costly strategy), expressed as cost per quality-adjusted life year (\$ per QALY). Analyses include outcomes related to cervical cancer and genital warts among females. All costs are expressed in 2006 U.S. dollars.

† All strategies include current cytology screening (see Methods section in main manuscript for details).

### EFFECT OF REVISED CERVICAL CANCER SCREENING POLICIES \*

Strategy	Base Case †	Revised Screening ‡ (3-year)	Revised Screening ‡ (5-year)
Screening alone	--	--	--
Vaccination (age 12)	43,600	40,900	28,200
Vaccination (age 12) + catch-up (13-18)	97,300	103,500	68,900
Vaccination (age 12) + catch-up (13-21)	120,400	128,700	89,000
Vaccination (age 12) + catch-up (13-26)	152,700	185,400	123,500

\* Values represent incremental cost-effectiveness ratios (additional cost divided by additional health benefit compared to the next-less-costly strategy), expressed as cost per quality-adjusted life year (\$ per QALY). All analyses include outcomes related to cervical cancer only. All costs are expressed in 2006 U.S. dollars.

† The base-case analysis assumes current cytology screening (see Methods section in main manuscript for details).

‡ The analyses assume cytology with HPV DNA testing as triage starting at age 25, with a switch to cytology combined with HPV DNA testing starting at age 35, every 3 or every 5 years.

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