ONLINE APPENDIX

Cervical cancer screening adherence in the era of HPV vaccination: how low is too low?

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Derivation and analysis of type-structured model

Parameter definitions

Here we consider a version of the model that is structured into two groups: vaccine-included HPV types 16/18, and other high-risk types.

We let $n_{16/18}$ denote the number of women at risk of cervical cancer due to current infection by vaccine-included types 16 and 18. We let n_{OHR} denote the number of women who are at risk of cervical cancer due to current infection by other high-risk types not included in the vaccine.

Similarly, we let $H_{16/18}^{pre}$ denote the rate at which women enter the at risk population due to infection by types 16 and 18 in the pre-vaccine, and we let H_{OHR}^{pre} denote the rate at which women enter the at risk population due to infection by other high-risk types not included in the vaccine. $H_{16/18}^{post}$ and $H_{16/18}^{post}$ are similarly defined for the vaccine era.

As in the main text, we let s denote the rate of screening (and treatment where applicable) per capita, and we let r denote the rate of removal from the at risk population due to natural regression, benign hysterectomy, and mortality. We also let f denote the vaccine

coverage, $e_{16/18}$ denote the clinical efficacy against types 16/18, and we let x denote the factor by which screening of vaccinated women drops relative to the pre-vaccine rate s.

Model equations

In this case the analogous equations for Equation (A1), representing the number of high-risk type 16/18 and other high-risk infections before the vaccine era, are:

(A5) $$\frac{dn_{16/18}}{dt} = H_{16/18}^{pre} - (r+s)n_{16/18}$$

(A6) $$\frac{dn_{OHR}}{dt} = H_{OHR}^{pre} - (r+s)n_{OHR}$$

which have the pre-vaccine era equilibria $n_{16/18}^{pre}$ and n_{OHR}^{pre} respectively:

(A7) $$n_{16/18}^{pre} = \frac{H_{16/18}^{pre}}{r+s}$$

(A8) $$n_{OHR}^{pre} = \frac{H_{OHR}^{pre}}{r+s}$$

The introduction of vaccination requires introducing parameters for vaccine coverage f, clinical vaccine efficacy $e_{16/18}$ against 16/18, and reduced screening frequency in vaccinated women of x. We also distinguish between number of vaccinated women infected with either 16/18 or other high-risk types, and number of unvaccinated women infected with either 16/18 or other high-risk types. Therefore Equations (A5) and (A6) in the vaccine era, and their equilibria, become:

(A9) $$\frac{dn_{16/18}^{novacc}}{dt} = H_{16/18}^{post}(1-f) - (r+s)n_{16/18}^{novacc} \Rightarrow n_{16/18}^{post,novacc} = \frac{(1-f)H_{16/18}^{post}}{r+s}$$

(A10) $$\frac{dn_{16/18}^{vac}}{dt} = H_{16/18}^{post}\left(f(1-e_{16/18})\right) - \left(r+sx\right)n_{16/18}^{vac} \Rightarrow n_{16/18}^{post,vac} = \frac{\left(f(1-e_{16/18})\right)H_{16/18}^{post}}{r+sx}$$

(A11) $$\frac{dn_{OHR}^{novac}}{dt} = (1-f)H_{OHR}^{post} - \left(r+s\right)n_{OHR}^{novac} \Rightarrow n_{OHR}^{post,novac} = \frac{(1-f)H_{OHR}^{post}}{r+s}$$

(A12) $$\frac{dn_{OHR}^{vac}}{dt} = fH_{OHR}^{post} - \left(r+sx\right)n_{OHR}^{vac} \Rightarrow n_{OHR}^{post,vac} = \frac{fH_{OHR}^{post}}{r+sx}$$

<u>Assumptions about type-replacement effects: change in prevalence of other high-risk types</u>

In the vaccine era we make the assumption that

(A13) $H_{16/18}^{post} = H_{16/18}^{pre}$

however this is conservative, since herd immunity implies that $H_{16/18}^{post} < H_{16/18}^{pre}$. We also let

(A14) $H_{OHR}^{post} = mH_{OHR}^{pre}$

where *m* captures type replacement effects and *m*>1. Therefore, the equilibrium solutions in equations (A9)-(A12) become

(A15) $$n_{16/18}^{post,novacc} = \frac{\left(1-f\right)H_{16/18}^{pre}}{r+s}$$

(A16) $$n_{16/18}^{post,vac} = \frac{\left(f(1-e_{16/18})\right)H_{16/18}^{pre}}{r+sx}$$

(A17) $$n_{OHR}^{post,novac} = \frac{(1-f)mH_{OHR}^{pre}}{r+s}$$

(A18) $$n_{OHR}^{post,vac} = \frac{fmH_{OHR}^{pre}}{r+sx}$$

<u>Assumptions about type-replacement effects: change in cancer cases due to lack of 16/18-associated lesion treatment in the vaccine era</u>

The table below defines parameters that control the pathogenicity of types.

Parameter	Definition
$O_{16/18}^{pre}$	the proportion of infections by types 16/18 that are undetected and that persist and eventually lead to cervical cancer, in the pre-vaccine era
O_{OHR}^{pre}	proportion of infections by other high-risk types that are undetected and that persist and eventually lead to cervical cancer, in the pre-vaccine era
$O_{16/18}^{post,vacc}$	proportion of infections by types 16/18 that are undetected and that persist and eventually lead to cervical cancer in vaccinated women, in the vaccine era
$O_{OHR}^{post,vacc}$	proportion of infections by other high-risk types that are undetected and that persist and eventually lead to cervical cancer in vaccinated women, in the vaccine era
$O_{16/18}^{post,unvac}$	proportion of infections by types 16/18 that are undetected and that persist and eventually lead to cervical cancer in unvaccinated women, in the vaccine era
$O_{OHR}^{post,unvac}$	proportion of infections by other high-risk types that are undetected and that persist and eventually lead to cervical cancer in unvaccinated women, in the vaccine era

Therefore in the pre-vaccine era, we can express the total incidence of cancer cases as

(A19) $$C^{pre} = O_{16/18}^{pre} n_{16/18}^{pre} + O_{OHR}^{pre} n_{OHR}^{pre}$$

Likewise we can express the total incidence of cancer cases in the vaccine era as

(A20) $$\begin{aligned} C^{post} &= O_{16/18}^{post,novac} n_{16/18}^{post,novac} + O_{OHR}^{post,novac} n_{OHR}^{post,novac} \\ &+ O_{16/18}^{post,vacc} n_{16/18}^{post,vacc} + O_{OHR}^{post,vacc} n_{OHR}^{post,vacc} \end{aligned}$$

Population-level and individual-level perversity emerge in the vaccine era if

(A21) $$C^{pre} < C^{post}$$

Substituting Equations (A7), (A8), (A15)-(A20) into Equation (A21) yields

(A22) $$\begin{aligned} O_{16/18}^{pre} \frac{H_{16/18}^{pre}}{r+s} + O_{OHR}^{pre} \frac{H_{OHR}^{pre}}{r+s} < O_{16/18}^{post,novac} \frac{(1-f)H_{16/18}^{pre}}{r+s} + O_{OHR}^{post,novac} \frac{(1-f)mH_{OHR}^{pre}}{r+s} \\ + O_{16/18}^{post,vac} \frac{f(1-e)H_{16/18}^{pre}}{r+sx} + O_{OHR}^{post,vac} \frac{fmH_{OHR}^{pre}}{r+sx} \end{aligned}$$

For oncogenicity of undetected infection, by type, we make the following assumptions:

(A23) $$O_{16/18}^{post,novacc} = O_{16/18}^{pre}$$

(A24) $$O_{OHR}^{post,novacc} = O_{OHR}^{pre}$$

since the natural history in unvaccinated women should not be significantly different from that in the pre-vaccine era. Equation (A22) thereby becomes

(A25)
$$O_{16/18}^{pre}\frac{H_{16/18}^{pre}}{r+s}+O_{OHR}^{pre}\frac{H_{OHR}^{pre}}{r+s}<O_{16/18}^{pre}\frac{(1-f)H_{16/18}^{pre}}{r+s}+O_{OHR}^{pre}\frac{(1-f)mH_{OHR}^{pre}}{r+s}$$
$$+O_{16/18}^{post,vac}\frac{f(1-e)H_{16/18}^{pre}}{r+sx}+O_{OHR}^{post,vac}\frac{fmH_{OHR}^{pre}}{r+sx}$$

which then simplifies to

(A26)
$$\left(\frac{1}{r+s}\right)\left(fO_{16/18}^{pre}H_{16/18}^{pre}+(1-m+mf)O_{OHR}^{pre}H_{OHR}^{pre}\right)<\left(\frac{1}{r+sx}\right)\left(f(1-e)O_{16/18}^{post,vac}H_{16/18}^{pre}+mfO_{OHR}^{post,vac}H_{OHR}^{pre}\right)$$

We also assume

(A27)
$$O_{OHR}^{pre}=\frac{1}{13}O_{16/18}^{pre}$$

which holds because, as noted in the main text, there were 13 times as many cases of cervical cancer per type 16/18 infection as per infections by other high-risk types in the United States, before vaccination was introduced. Also, we assume that

(A28)
$$O_{16/18}^{post,vac}=O_{16/18}^{pre}$$

since the proportion of infections by types 16/18 with the potential to result in cervical cancer should be the same for women in the pre-vaccine era versus for women who were vaccinated unsuccessfully. Finally, we will let

(A29)
$$O_{OHR}^{post,vacc}=\frac{1}{13}kO_{16/18}^{pre}$$

where k is an adjustment factor reflecting the differing oncogenicity for types 16/18 before the vaccine era versus the oncogenicity for other high-risk types in the vaccine era. Generally, we expect that $k>1$ because vaccination for types 16/18 prevents treatments

that would previously have removed slower-progressing other high-risk types in the pre-vaccine era. Applying assumptions (A27)-(A29) to Equation (A26) yields:

$$\text{(A30)} \qquad \left(\frac{1}{r+s}\right)\left(fH_{16/18}^{pre}+\frac{1}{13}(1-m+mf)H_{OHR}^{pre}\right)<\left(\frac{1}{r+sx}\right)\left(f(1-e)H_{16/18}^{pre}+\frac{1}{13}mfkH_{OHR}^{pre}\right)$$

Moreover, using the relation that prevalence = incidence x duration, assuming that the average duration of infection by types 16/18 is the same as the average duration of infection by other types, and using the type-specific prevalence reported in the main text, we have that $H_{OHR}=\frac{12.9}{2.3}H_{16/18}=5.6H_{16/18}$. So, Equation (A30) reduces to

$$\text{(A31)} \qquad \left(\frac{1}{r+s}\right)\left(f+\frac{5.6}{13}(1-m+mf)\right)<\left(\frac{1}{r+sx}\right)\left(f(1-e)+\frac{5.6}{13}mfk\right)$$

Which in turn reduces to a condition on the threshold x^*:

$$\text{(A31)} \qquad x^*=\left(\frac{r+s}{s}\right)\left(\frac{f(1-e)+0.43mfk}{f+0.43(1-m+mf)}\right)-\frac{r}{s}$$

Finally, from the main text, we have at baseline values that s=0.44 per year, r=0.83 per year, and e=0.95. Therefore equation (A31) becomes:

$$\text{(A32)} \qquad x^*=2.89\left(\frac{0.1f+0.43mfk}{f+0.43(1-m+mf)}\right)-1.89$$

Tables A1 and A2 below provide threshold values x^* calculated from Equation (A32) for various values k and m, for the cases f=0.50 and f=0.90 respectively. The results are mostly insensitive to vaccine coverage. In the case where type replacement effects increase the prevalence of other high-risk types by 10%, the screening threshold exceeds the estimate x^*=0.61 from the main text only when the oncogencity (proportion of high-risk infections that eventually develop into cervical cancer) of high-risk types increases

by at least 175%. Since other high-risk types actually progress more slowly than types 16/18, the true required increase is likely much higher than this. In the less likely case where type replacement increases the prevalence of other high-risk types by 50%, the required increase in oncogenicity is about 50%. We also note that we make the conservative assumption of ignoring herd immunity, and we assume that the progression rate of other high-risk types equals that of types 16/18.

Table A1: Values of x^* at 50% vaccine coverage. Shaded blue cells denote closest values to x^*=0.61 estimate from main text.

		m					
		1.0	1.1	1.2	1.3	1.4	1.5
k	1.0	0	0	0	0	0	0
	1.1	0	0	0	0	0	0
	1.2	0	0	0	0	0	0.07
	1.3	0	0	0	0	0.02	0.22
	1.4	0	0	0	0	0.16	0.38
	1.5	0	0	0	0.08	0.30	0.53
	1.6	0	0	0	0.21	0.44	0.68
	1.7	0	0	0.10	0.33	0.58	0.84
	1.8	0	0	0.21	0.46	0.71	0.99
	1.9	0	0.09	0.33	0.58	0.85	1
	2.0	0	0.19	0.44	0.70	0.99	1
	2.1	0.04	0.29	0.55	0.83	1	1
	2.2	0.12	0.39	0.66	0.95	1	1
	2.3	0.21	0.49	0.77	1	1	1
	2.4	0.30	0.58	0.88	1	1	1
	2.5	0.38	0.68	0.99	1	1	1
	2.6	0.47	0.78	1	1	1	1
	2.7	0.56	0.88	1	1	1	1
	2.8	0.64	0.97	1	1	1	1
	2.9	0.73	1	1	1	1	1
	3.0	0.82	1	1	1	1	1

Table A2: Values of x^* at 90% vaccine coverage. Shaded blue cells denote closest values to x^*=0.61 estimate from main text.

		m					
		1.0	1.1	1.2	1.3	1.4	1.5
k	1.0	0	0	0	0	0	0
	1.1	0	0	0	0	0	0
	1.2	0	0	0	0	0	0
	1.3	0	0	0	0	0	0
	1.4	0	0	0	0	0	0.07
	1.5	0	0	0	0	0.06	0.20
	1.6	0	0	0	0.04	0.19	0.33
	1.7	0	0	0	0.15	0.31	0.47
	1.8	0	0	0.10	0.27	0.43	0.60
	1.9	0	0.03	0.21	0.38	0.56	0.73
	2.0	0	0.13	0.31	0.49	0.68	0.86
	2.1	0.04	0.23	0.42	0.61	0.80	1
	2.2	0.12	0.32	0.52	0.72	0.93	1
	2.3	0.21	0.42	0.63	0.84	1	1
	2.4	0.30	0.51	0.73	0.95	1	1
	2.5	0.38	0.61	0.84	1	1	1
	2.6	0.47	0.71	.94	1	1	1
	2.7	0.56	0.80	1	1	1	1
	2.8	0.64	0.90	1	1	1	1
	2.9	0.73	0.99	1	1	1	1
	3.0	0.82	1	1	1	1	1