Supplementary

Simultaneously characterizing the comparative economics of routine female adolescent nonavalent human papillomavirus (HPV) vaccination and assortativity of sexual mixing in Hong Kong Chinese: a modeling analysis

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Sexual mixing

We use the survey data published by the FPAHK (http://www.famplan.org.hk) to construct the sexual activity matrix (Table S1) as follows:

1. Individuals age below 10 or above 69 are assumed to be sexually inactive.
2. The sexual activity distributions for individuals age 13-14 (text in red) are based on the data for Forms 1-2 students in The Report of Youth Sexuality Study 2011.
3. The sexual activity distributions for individuals age 10-12 (text in green) are linearly interpolated from the distributions in steps 1 and 2.
4. The sexual activity distributions for individuals age 15-19 (text in purple) are based on the data in Section Form 3- Form 7 in The Report of Youth Sexuality Study 2006.
5. The sexual activity distributions for individuals age 20-24 (text in magenta) are based on the data in Section Aged 18-27 Youths in The Report of Youth Sexuality Study 2006.
6. The sexual activity distributions for males age 30-69 (text in blue) are based on Table 7.5a in the 2001 Men's Health Survey.
7. The sexual activity distributions for females age 30-69 (text in orange) are extrapolated from the distribution for females age 20-24 (from step 5) assuming that the age effect on the distribution of low and high levels of sexual activity for females is the same as that for males (from step 6).
8. The data in both The Report of Youth Sexuality Study 2006 and Men's Health Survey 2001 suggest that those with a high level of sexual activity had an average of 2.5 sexual partners during the past 6 months.

	Sexual activity level (no. of sexual partners during the 6 months)					
	Male			Female		
Age (years)	**None (0)**	**Low (1)**	**High (>1)**	**None (0)**	**Low (1)**	**High (>1)**
10-12	0.993	0.007	0.000	0.998	0.002	0.000
13-14	0.985	0.015	0.000	0.995	0.005	0.000
15-19	0.900	0.062	0.038	0.945	0.046	0.009
20-24	0.580	0.303	0.117	0.632	0.291	0.077
25-29	0.286	0.579	0.135	0.312	0.556	0.132
30-39	0.102	0.798	0.100	0.111	0.766	0.122
40-49	0.094	0.827	0.079	0.102	0.794	0.103
50-59	0.099	0.849	0.052	0.108	0.815	0.077
60-69	0.362	0.604	0.034	0.394	0.580	0.025

Table S1. The distribution of individuals with no, low and high level of sexual activity in each age group. Individuals with one and multiple sexual partners during the past 6 months are regarded as having low and high sexual activity levels, respectively.

Adjusted contact rates

For the transmission model to be internally consistent, the following balance rule must be satisfied at all times:

$$c_{f,a,u}\rho_{f,a,u,b,v}(t)N_{f,a,u}(t) = c_{m,b,v}\rho_{m,b,v,a,u}(t)N_{m,b,v}(t)$$

$$c_{f,a,u}\rho_{f,a,u,b,v}(t)N_{f,a,u}(t) = c_{m,b,v}\rho_{m,b,v,a,u}(t)N_{m,b,v}(t)$$

This balance rule simply states the fact that the number of sexual partnerships that females from stratum (f,a,u) form with males from stratum (m,b,v) is the same as the number of sexual partnerships that males from stratum (m,b,v) form with females from stratum (f,a,u). At any given time *t*, the degree to which the balance rule is violated could be measured by:

$$D_{a,u,b,v}(t) = \frac{c_{f,a,u}\rho_{f,a,u,b,v}(t)N_{f,a,u}(t)}{c_{m,b,v}\rho_{m,b,v,a,u}(t)N_{m,b,v}(t)}.$$

To ensure that the balance rule is satisfied at all times, the adjusted contact rates are:

$$c^{*}_{f,a,u,b,v}(t) = c_{f,a,u}\left(D_{a,u,b,v}(t)\right)^{-(1-\theta)}$$
$$c^{*}_{m,b,v,a,u}(t) = c_{m,b,v}\left(D_{a,u,b,v}(t)\right)^{\theta}$$

Following common practice, we choose $\theta = 0.5$ which means that the relevant parameters of females and males are adjusted to the same degree.[1]

Natural history

Figure S1 shows the natural history of HR-HPV infection and cervical cancer among females in the model. Individuals enter the population without HPV infection at birth and become sexually active as early as age 10. For females who are infected with HPV, the infection could progress to precancerous states (CIN1, CIN2 and CIN3). We assume that individuals with CIN3 would not recover naturally. Disease progression rates and clearance rates are assumed to depend on HPV type but not age.

Local cervical cancer without symptoms may become symptomatic or progress to more advanced stages of cervical cancer without symptoms. In the absence of screening, cervical cancer is diagnosed only when symptoms develop in which the patient is immediately treated. Females with symptomatic cervical cancer are subjected to stage-specific (local, regional or distant) probability of cancer-associated death.[2] We assume that recovery from cervical cancer does not confer natural immunity against reinfection. The progression rates of cervical cancer and the cervical cancer-related death rates are assumed to be independent of age, sexual activity level and HPV type.[3]

Basic compartmental epidemic models based on ordinary differential equations (ODEs) assume that the duration of each compartment is exponentially distributed.[4] For any given mean duration, the probability that the duration is shorter than the mean is higher in exponential distribution than in more biologically plausible distributions such as Erlang and lognormal distributions. Such a difference would have little effect for disease states milder than CIN3 because their durations are relatively short compared to cervical screening intervals. However, given that the expected duration of CIN3 is much longer (>10 years on

average),[5] assuming that the duration of CIN3 is exponentially distribution might artificially lower the effectiveness of cervical screening. As such, we assume that the time from CIN3 to asymptomatic local cervical cancer is an Erlang-4 distribution.[4,6] This multiple-compartment component is important for the stochastic cohort simulation model which simulates the impact of cervical screening on prevention of cervical cancer. We refer to a local study for cervical cancer specific survival by the International Federation of Gynaecologists and Oncologists (FIGO) staging system.[7] The reported 5-year survival rates are 90.9%, 71.0%, 41.7% and 7.8% for FIGO stage I, II, III and IV, respectively. Cancer patients who remain alive 5 years after cancer diagnosis are regarded as cancer survivors.[8] In the model, cancer survivors are moved to the health state "No infection (susceptible)" and are susceptible to new HPV infection.

We assume that the transmission, progression and regression parameters for HPV infections in males are the same as that in females.[3] We do not consider HPV-associated diseases among males.[3,9]

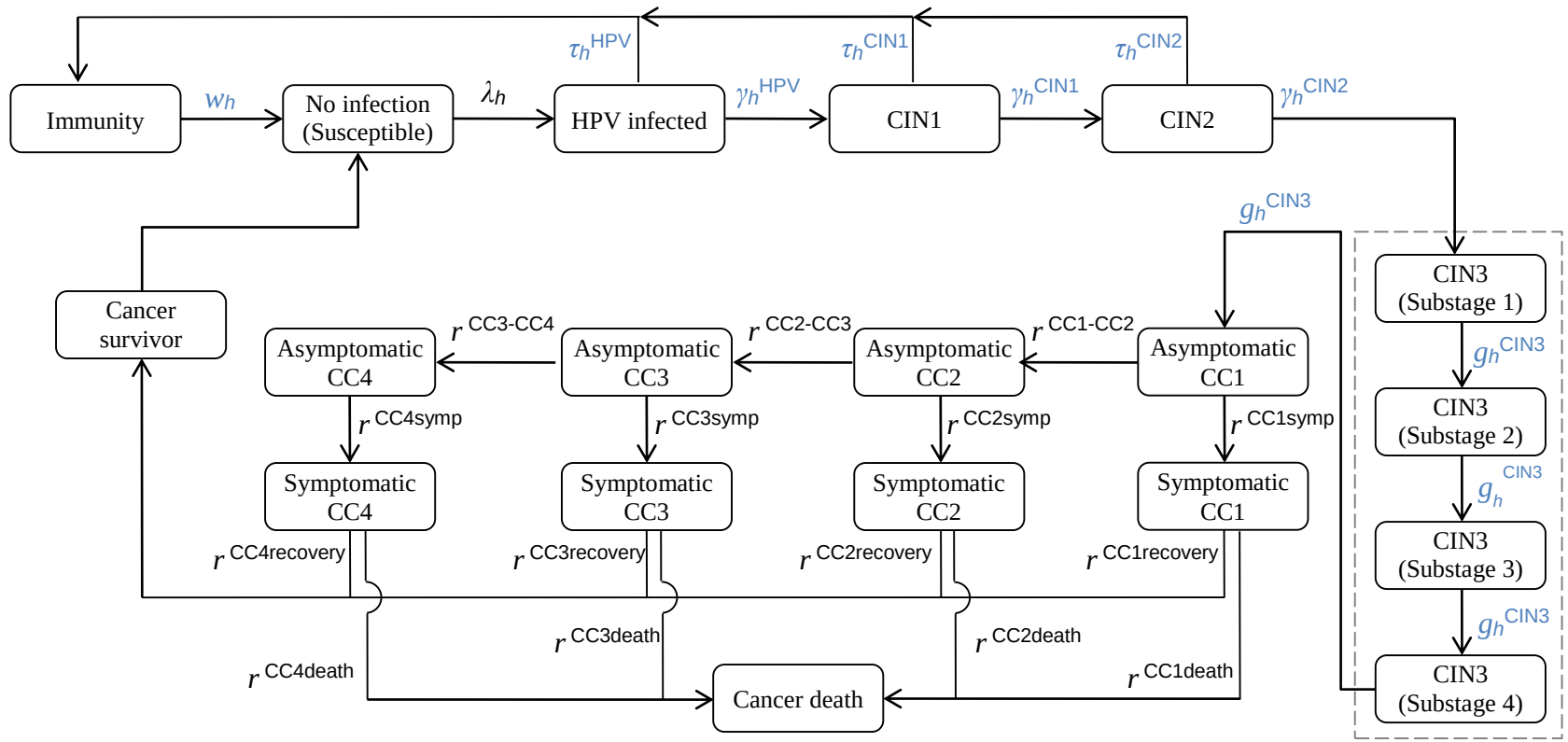

Figure S1. Schematic of the natural history model for HR-HPV infection and cervical cancer among females. Abbreviations: CC1 to CC4, cervical cancer in International Federation of Gynecology and Obstetrics (FIGO) stage I to IV correspondingly. λ_h is the force of infection (FOI) for HPV class h. γ_h^X and τ_h^X are the progression and clearance rate for disease state X with HPV class h. w_h is the waning rate of natural immunity against HPV class h. The progression of CIN3 to asymptomatic CC1 is assumed to follow an Erlang-4 distribution with mean $1/\gamma_h^{CIN3}$, i.e. $\gamma_h^{CIN3} = g_h^{CIN3} / 4$.

Model parameterization

We estimate the model parameter values using the Metropolis-Hasting algorithm with non-informative flat priors for all parameters[10,11] (see Table S2). When formulating the likelihood function for model fitting, we assume:

1. The data on age-specific HPV prevalence[12] and proportion of HPV types in cervical cancer cases[13] follow binomial distributions;
2. The data on age-specific cervical cancer incidence[14] follow Poisson distributions;
3. The data on disease progression and clearance (for different stages of HPV infection)[15,16] follow multinomial distributions.

The trace plot and Geweke diagnostic[17] indicate that the MCMC chain converges (Figure S2). As such, we estimate the posterior distribution by running the Metropolis-Hasting algorithm for 300,000 iterations with a burn-in of 150,000 iterations without thinning. Table S2 shows the summary statistics of the posterior distributions.

(A) Inferred parameters on natural history		Posterior median (95% CrI)			
Parameter	Description	HPV-16	HPV-18	HPV-OV	HPV-NV
β_h	Transmission probability per sexual partnership	0.75 (0.50, 0.96)	0.88 (0.60, 0.98)	0.93 (0.80, 0.99)	0.61 (0.50, 0.71)
$1/\gamma_h^{HPV}$	Mean duration: progression from HPV infection to CIN1	8.7 (7.2, 11.3)	5.9 (4.3, 8.6)	10.7 (8.9, 12.8)	11.2 (9.4, 13.5)
$1/\gamma_h^{CIN1}$	Mean duration: progression from CIN1 to CIN2	3.9 (2.7, 5.3)	3.4 (2.3, 5.2)	2.7 (2.1, 3.9)	
$1/\gamma_h^{CIN2}$	Mean duration: progression from CIN2 to CIN3	4.2 (3.0, 6.4)	4.2 (2.9, 6.7)	4.5 (2.9, 7.3)	
$1/\gamma_h^{CIN3}$	Mean duration: progression from CIN3 to cervical cancer	22 (18, 28)	22 (16, 30)	32 (20, 40)	
$1/\tau_h^{HPV}$	Mean duration: clearance of HPV infection	2.2 (1.9, 2.5)	1.4 (1.2, 1.7)	1.6 (1.5, 1.8)	1.6 (1.5, 1.7)
$1/\tau_h^{CIN1}$	Mean duration: clearance of CIN1	3.2 (2.1, 4.8)	3.0 (2.2, 4.3)	1.3 (1.1, 1.7)	
$1/\tau_h^{CIN2}$	Mean duration: clearance of CIN2	3.2 (2.5, 4.3)	3.2 (2.3, 4.4)	1.7 (1.4, 2.4)	
$1/w_h$	Mean duration of natural immunity	15.9 (2.7, 83.2)	16.9 (3.6, 74.8)	0.68 (0.51, 1.69)	0 (assumed)

(B) Inferred parameters on sexual mixing		Posterior median (95% CrI)
W_1	Age (yrs) at which susceptibility and infectiousness begin to fall	21 (16, 25)
W_2	Age (yrs) at which susceptibility and infectiousness stop falling and begin to plateau	24 (21, 27)
M	Relative transmission probability for individuals older than W_1	0.47 (0.41, 0.53)
ε_A	Degree of assortativeness for sexual mixing across ages	0.77 (0.29, 0.97)
ε_S	Degree of assortativeness for sexual mixing across sexual activity levels	0.98 (0.89, 0.99)
σ_g	Spread of age preference (yrs) in forming sexual partnership	2.05 (0.21, 4.90)

Table S2. Posterior distributions of inferred parameters.

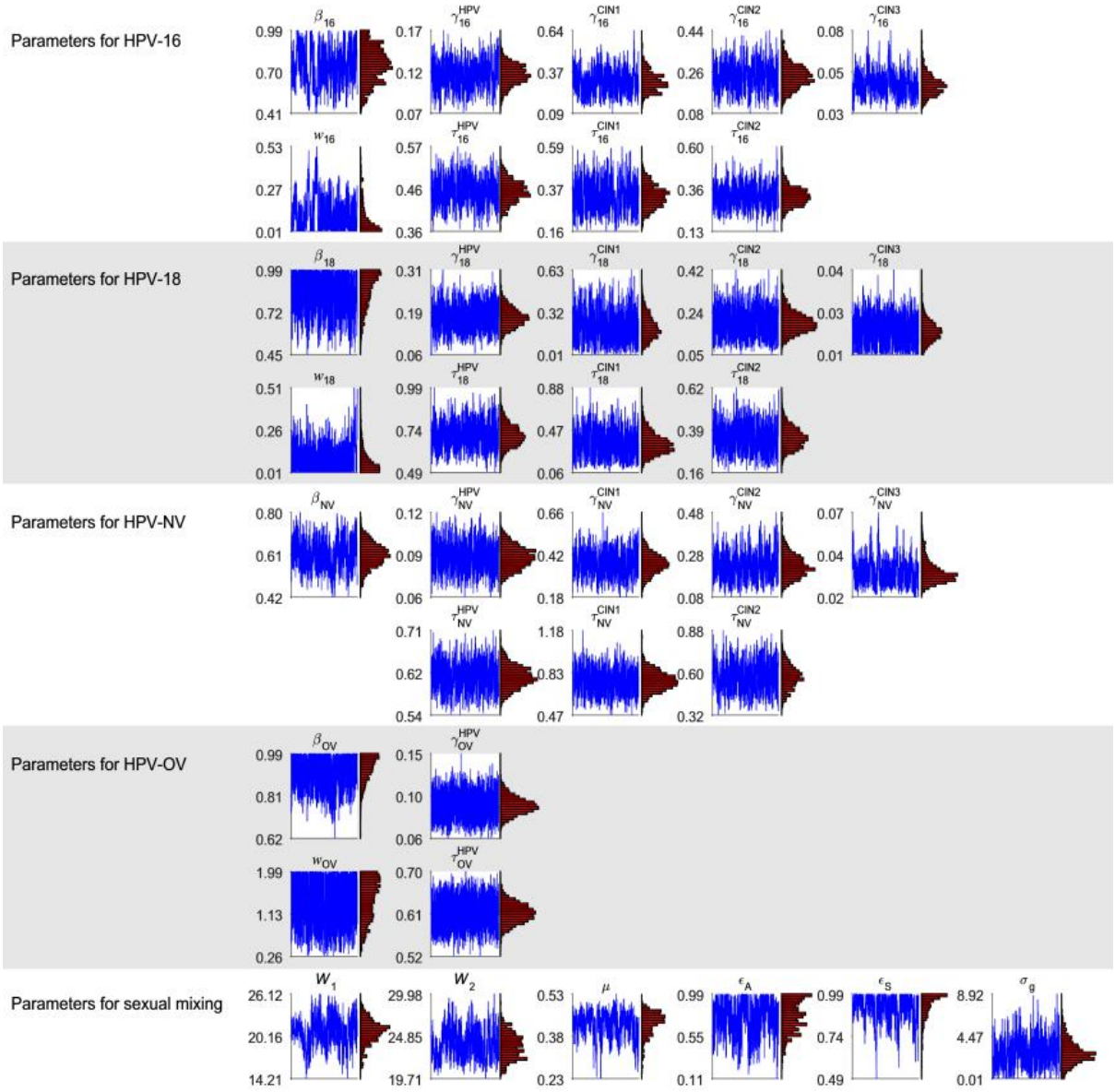

Figure S2. Trace plots and the posterior distributions of the fitted parameters.

Cervical screening

The Cervical Screening Programme (CSP) in Hong Kong was launched in 2004.[18] CSP recommends eligible women aged 25-64 to adopt 1-,1-,3-yearly cervical cytology screening, i.e. screening annually for their first two years of screening and then triennially if their screening results remain negative. The latest statistics from the Department of Health suggest that 70% of eligible women have had undergone screening at least once, 60% of whom have had their most recent screening episode during the last 3 years.[18] This finding is consistent with our previous survey in 2009.[19] As such, we make the following assumptions regarding the uptake of cervical cancer screening after CSP has launched in 2004:

i. 70% of females begin screening when they reach age 25;
ii. 60% of the females in (i) will then follow the 1-,1-,3-yearly screening;
iii. The remaining 40% of (i) will attend screening annually in the first 2 years and then every 75 months afterwards.[19]

We assume the following screening uptake before the launch of CSP [19]:

i. 40% of females begin screening when they reach age 25 years since 1980 when cervical screening was introduced into systematic antenatal care in Hong Kong;[19,20]
ii. 60% of the females in (i) attend screening regularly at 1- to 3-year interval;[19]
iii. The screening uptake increases linearly from 40% in 1980 to 70% in 2004 when CSP was launched.[18]

Table S3 summarizes (a) sensitivity and specificity of cervical cytology and (b) the probability of cytology results given the true health states assumed in our analysis.[21-23] Furthermore, we set the sensitivity of colposcopy to CIN1 and CIN2/3 lesions at 81%, based

on the findings from the two cervical screening trials in China.[24,25] We assume same sensitivity to CIN lesions as suggested by another overseas study.[26] We set the sensitivity of colposcopy to cervical cancer at 100%. We also set 100% sensitivity of biopsy to CIN lesions and cervical cancers.

Test characteristic for cervical cytology[21]	**Distribution**	**References**
Sensitivity		
CIN1	T(0.70, 0.50. 1.00)	[21]
CIN2/3	T(0.80, 0.50. 1.00)	[21]
Cervical cancer	T(1.00, 0.95, 1.00)	Assumed
Specificity	T(0.95, 0.90. 1.00)	[21]

Table S3a. Probability distributions of cervical cytology testing. *T*(*a*,*b*,*c*) denotes triangular distribution that ranges from *b* to *c* with mode *a*.

Probability of cytology results				
	True health states			
Cytology results	Normal	CIN1	CIN2/3	Cancer
ASCUS	0.704	0.517	0.380	0.286
LSIL	0.269	0.448	0.450	0.286
HSIL	0.027	0.035	0.170	0.428

Table S3b. Probability of cytology results given true health states. Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion. Ref.: [21-23].

Cost parameters

We estimate that the costs for screening and treatments based on the private charges in the public healthcare system (released by the Department of Health and listed in the 2013 Gazette[27]) which accounts for approximately 90% of hospitalization in Hong Kong.[28] Table S4 summarizes the probability distributions of the costs used in our analysis. The underlying assumptions are provided below.

The costs of screening comprise:

1. The cost of cytology Pap smear for routine screening;
2. The cost of colposcopy for the follow-up of low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) after abnormal Pap smear.
3. Time and transportation cost for women to go to clinics for screening, where the time cost is based on the average income of females by age groups.[29,30]

We estimate the treatment costs for CIN2/3 and cervical cancer based on public hospital charges for private patients with standard treatments (i.e. assuming that the public hospitals make these charges just for covering their costs instead of making profits).[27] The private charges for in-patients include the fees for general nursing, core pathology investigations, catering and also domestic services.[31] The treatment cost of cervical cancer comprises the cost of hospitalization for receiving Wertheim's hysterectomy, brachytherapy, and overnight infusion chemotherapy. We assume 67.4% of the women who die from cervical cancer would receive palliative care with a mean hospitalization duration of 42.5 days.[32]

Cost	Distribution (USD)	References
Cytology test	N(67.9, 17)	[27]
Colposcopy + biopsy	N(779, 195)	[27]
Treatment for CIN2 or CIN3 Loop electro-surgical excision procedure (LEEP)	N(1869, 467)	[27]
Treatment for local cervical cancer Wertheim's hysterectomy	N(13,914, 3,479)	[27]
Treatment for regional cervical cancer Radiotherapy + chemotherapy + brachytherapy	N(31,051, 7,763)	[27]
Treatment for distant cervical cancer Palliative radiotherapy + palliative chemotherapy	N(23,476, 5,869)	[27]
Palliative care (per day)	T(601, 479, 723)	[27,32]
Time cost (half day)	N(30.1, 7.5)	[33]
Transportation	N(6.4, 1.6)	[29]

Table S4. Probability distributions of cost parameters. $N(a,b)$ denotes normal distribution with mean a and standard deviation b. $T(a,b,c)$ denotes triangular distribution that ranges from b to c with mode a.

Cost-benefit analysis

We use the human capital approach to estimate the productivity loss incurred due to (i) screening, (ii) treatment for cervical intraepithelial lesions and cervical cancer, and (iii) premature death from cervical cancer.[34] These productivity losses comprise (i) loss of economic income that would have been earned by the individual and (ii) loss of workplace productivity (for the individual's employer) that would have been averted if the individual has not experienced these events.[35] Nicholson et al. (2006) estimated that the absence of an employee would generate an extra loss of 61% times the employee's income to the employer and thus to the entire society, i.e. a wage multiplier of 1.61.[35] When estimating productivity loss for different age groups, we adjust for the age-specific unemployment and labor force participation rate.[36] Specifically, given age group i, let w_i be the average daily income for employed persons, r_{ui} be the unemployment rate, r_{fi} be the labor force participation rate, and m_w be the wage multiplier. The adjusted potential daily productivity loss from a female in that age group i is $w_i m_w r_{fi}(1-r_{ui})$.

We make the following assumptions regarding the duration of productivity loss:

1. Each episode of screening is associated with 2 days of absence from work: 1 day for attending screening and 1 day for reviewing the screening result.
2. Each episode of CIN2/3 treatment is associated with 3 days of absence from work: 1 day for receiving the treatment and 2 days for resting.
3. Treatment of cervical cancer is associated with 6 months of absence from work for local, regional and distant stage.[8]
4. Premature death from cervical cancer is associated with absence from work between the time of death and the average retirement age which we assume to be 65 years.[33]

Cost-effectiveness analysis

When calculating quality-adjusted life-years (QALYs), we rely on health utility parameters from overseas HPV vaccination cost-effectiveness studies (Table S5) because analogous data are not available in Hong Kong.[21,37,38] QALY is estimated by summing women's health utilities incurred throughout their lifetimes. We assume that there is no health utility loss for undiagnosed or asymptomatic cervical lesions and cervical cancer.[39] Health utility is reduced (i) upon abnormal screening results; (ii) upon diagnosis and treatment (if any) of CIN; and (iii) during treatment of cervical cancer. Furthermore, we assume that cancer survivors have lower health utilities for their first 5 years after recovery.[8]

There is no consensus on willingness-to-pay threshold below which health interventions are deemed cost-effective in Hong Kong. As such, we use GDP per capita (approximately US$40,099 for Hong Kong during 2012-2016[40]), as the societal willingness-to-pay threshold.

Health utility	Distribution	References
Screening	N(0.98, 0.005)	[38]
ASCUS	N(0.94, 0.015)	[38]
Normal colposcopy result	N(0.95, 0.013)	[38]
CIN1	N(0.81, 0.022)	[38]
CIN2/3	N(0.87, 0.033)	[38]
Local cervical cancer	T(0.65, 0.49, 0.81)	[41]
Regional cervical cancer	T(0.56, 0.42, 0.70)	[41]
Distant cervical cancer	T(0.48, 0.36, 0.60)	[41]
Cancer survivor	T(0.62–0.97, 0.47–0.73, 0.78–0.99)	[41]

Table S5. Probability distribution of QALY weights for different health outcomes. $N(a,b)$ denotes normal distribution with mean a and standard deviation b. $T(a,b,c)$ denotes triangular distribution that ranges from b to c with mode a. Standard deviations for health utilities were based on the corresponding utility detriments from perfect health (i.e., 1) and an assumption of 0.25 coefficient of variation (CV).[42]

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