Cost benefit analysis of routine female adolescent HPV vaccination for reducing the economic burden of cervical cancer in Hong Kong

Horace Choi, Mark Jit, Gabriel M Leung, Joseph T Wu

SCHOOL OF PUBLIC HEALTH
THE UNIVERSITY OF HONG KONG
香 港 大 學 公 共 衞 生 學 院

WHO Collaborating Centre
for Infectious Disease Epidemiology and Control

Human papillomavirus (HPV) vaccines

- The 9-valent HPV vaccine is nearly 100% protective against:
  - 7 types of high-risk HPV (16 18, 31, 33, 45, 52 and 58) which cause 85-95% of cervical cancer (CC)
  - 2 types of low-risk HPV (6 and 11) which cause more than 90% of genital warts
- The WHO recommended that cost-effectiveness of HPV vaccination strategies should be considered before including HPV vaccination in national programs.
- The cost-effectiveness of routine female adolescent HPV vaccination and other strategies (e.g. vaccinating male adolescents as well) has been extensively studied for many high-income countries (e.g. the UK, Australia, Canada) as well as middle- and low-income countries (e.g. Malaysia, Brazil, Peru).
- The consensus among these studies is that routine female adolescent HPV vaccination using the 4-valent or 2-valent vaccine is cost-effective.

The state of cervical cancer prevention in Hong Kong

- Among females aged 25-64:
  - Only 69% have ever had a cervical smear
  - Only 57% had her last cervical smear taken within the last 3 years
  - Only 20% have registered with Cervical Screening Program

- Around 9% of adolescent girls have received HPV vaccination

- Our cost-effectiveness analysis (CEA) in 2013 suggested that routine female adolescent HPV vaccination using 4-valent or 2-valent vaccine would very likely be cost-effective.

- The cost-benefit of routine female adolescent HPV vaccination has never been rigorously evaluated for any population. Such cost-benefit analysis (CBA) could complement CEA and is needed for health policymaking in some jurisdictions.

Objective

To characterize the cost-benefit of routine female adolescent HPV vaccination compared to opportunistic vaccination with status quo vaccine uptake (~9%):

1. Routine vaccination for girls at age 12 (RV)
2. RV + 2 years of catch-up vaccination for girls age 13-18 (RV+C)

Health burden: Cervical cancer only, i.e. not considering genital warts

Outcome: *Threshold vaccine cost*, the maximum cost for fully immunizing one girl at which the HPV vaccination strategy under consideration is cost-beneficial

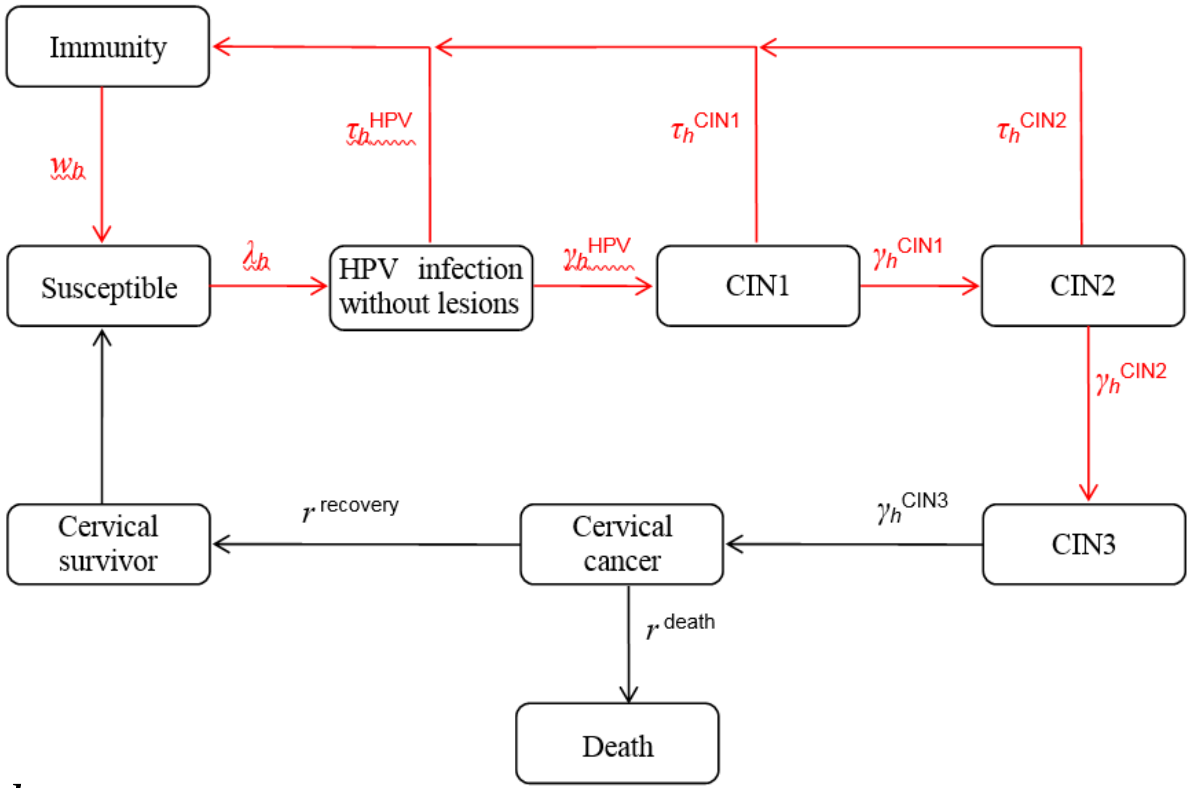
Methods for CBA: (i) Human capital approach; (ii) Quality adjust life years (QALY) monetization with one GDP per capita as the conversion factor (i.e. equivalent to CEA)

Time horizon: 100 years with 3% annual discount for both costs and health utilities

Natural history model for HPV infection and cervical lesions

Four high-risk HPV classes:

- HPV-16
- HPV-18
- Other HPV vaccine types (HPV-OV, which comprises 31, 33, 45, 52 and 58)
- HPV non-vaccine high-risk types (HPV-NV)



- λ_h is the force of infection (FOI) for HPV class h
- γ_h^X and τ_h^X are the progression and recovery rate for disease stage X with HPV class h, respectively
- w_h is the waning rate of natural immunity for HPV class h
- $r^{recovery}$ and r^{death} are cancer stage-specific recovery and death rates (not dependent on HPV class)

Model for HPV transmission and cervical cancer development

A hybrid model with two components:

1. A deterministic age-structured compartmental dynamic model for simulating heterosexual transmission of high-risk HPV
   - Generate the force of infection (FOI) of the four HPV classes after routine female adolescent HPV vaccination has begun.
   - Parameterize the model (“fitting the model to data”)

2. A stochastic individual-based cohort model for simulating the development of cervical cancer over the lifetime of each female
   - The FOI outputted by the dynamic model is fed into this stochastic individual-based model to simulate cervical cancer incidence for each female in the presence of cervical screening

Sexual mixing

The age-specific sexual activity matrix is based on local sexuality surveys conducted by the Family Planning Association of Hong Kong.

	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		0.009
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

Model parameterization

Parameters to be estimated:

i. Progression and recovery rates for all stages of HPV infection (class-specific);
ii. Transmission probability per sexual partnership (class-specific)
iii. Waning rate of natural immunity (class-specific)
iv. Sexual mixing parameters

Data for model fitting:

1. Age-specific prevalence of HPV-16, 18, OV and NV in Hong Kong
   - Private communication with Prof Paul Chan and Hextan Ngan for their raw data in *Chan et al* 2002 and *Liu et al* 2011.
2. Age-specific CC incidence in 1980-1984 as recorded in the Hong Kong Cancer Registry
   - This period was chosen in order to minimize the confounding effect of screening on cervical cancer incidence
3. HPV type distribution among CC cases diagnosed in two major Hong Kong hospitals (*Chan et al* 2012)
4. The cumulative proportion of cases with disease progression and recovery for different stages of HPV infection (over a period of 2 years) from two oversea studies (*Insinga et al* 2011, *Moscicki et al* 2010). Analogous data are not available in Hong Kong.

Parameter estimation / Statistical inference

- The model is fitted to the data using Markov Chain Monte Carlo method

- Non-informative uniform priors are used for all parameters

- Standard formulation for the likelihoods, e.g. the likelihood for the prevalence of HPV class h is

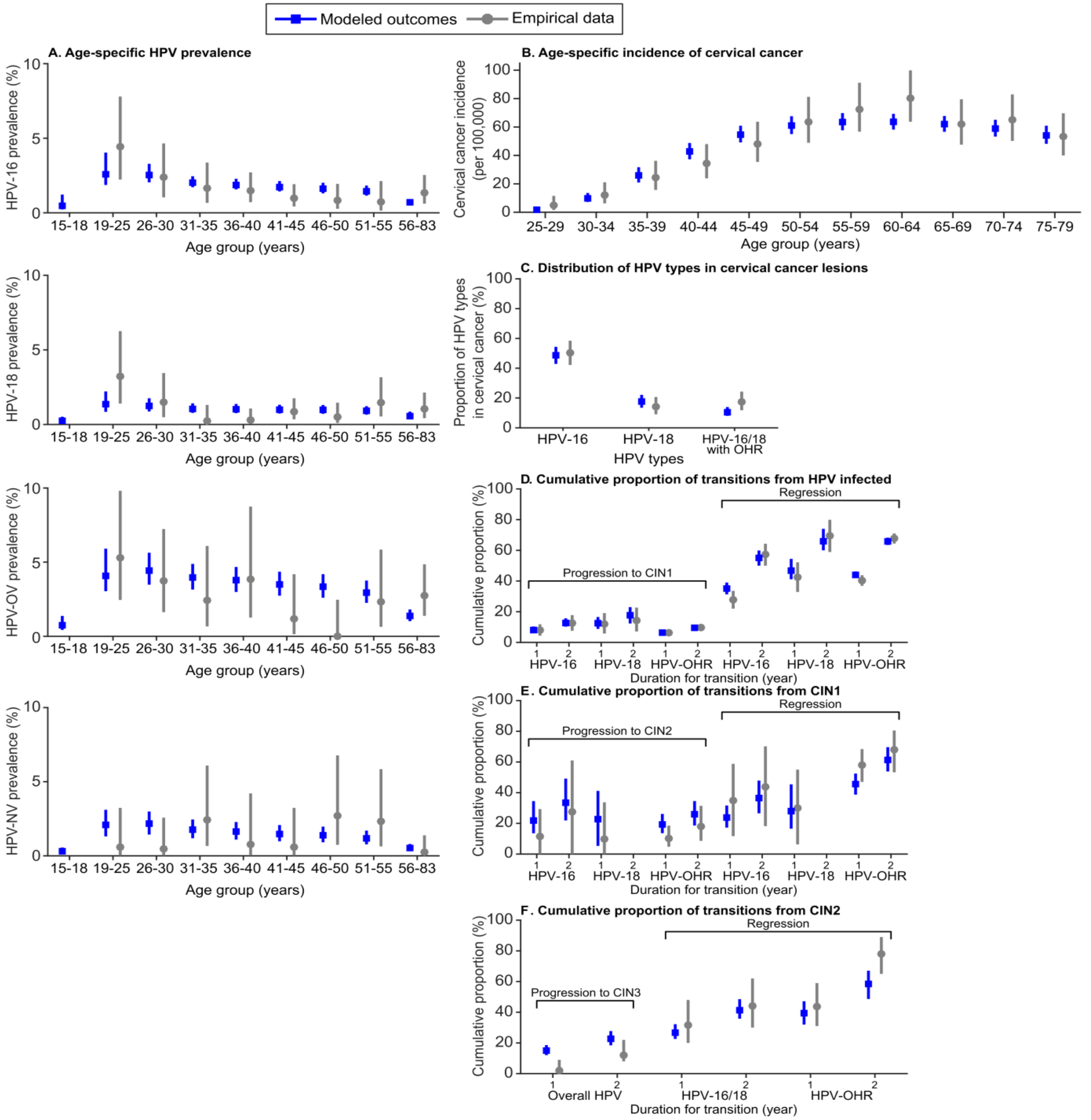
$$Binomial(n_a, x_{a,h},, p_{a,h}\,(\theta))$$

a

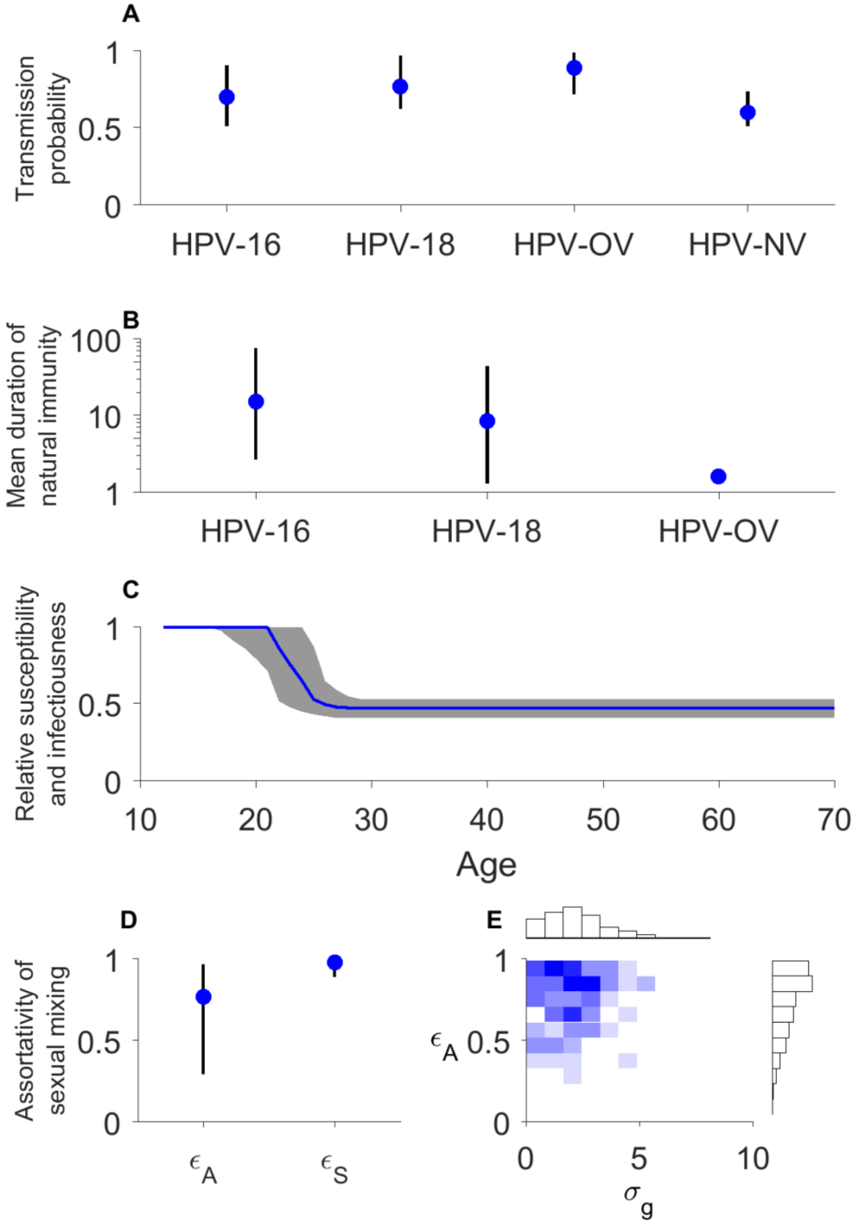
where n_a is the number of specimens in age group a, $x_{a,h}$ is the number of such specimens that are positive for HPV class h, and $p_{a,h}$ is the prevalence of HPV class h in age group a when the model parameters are θ.

- The resulting posterior distribution is used for probabilistic sensitivity analysis (PSA).

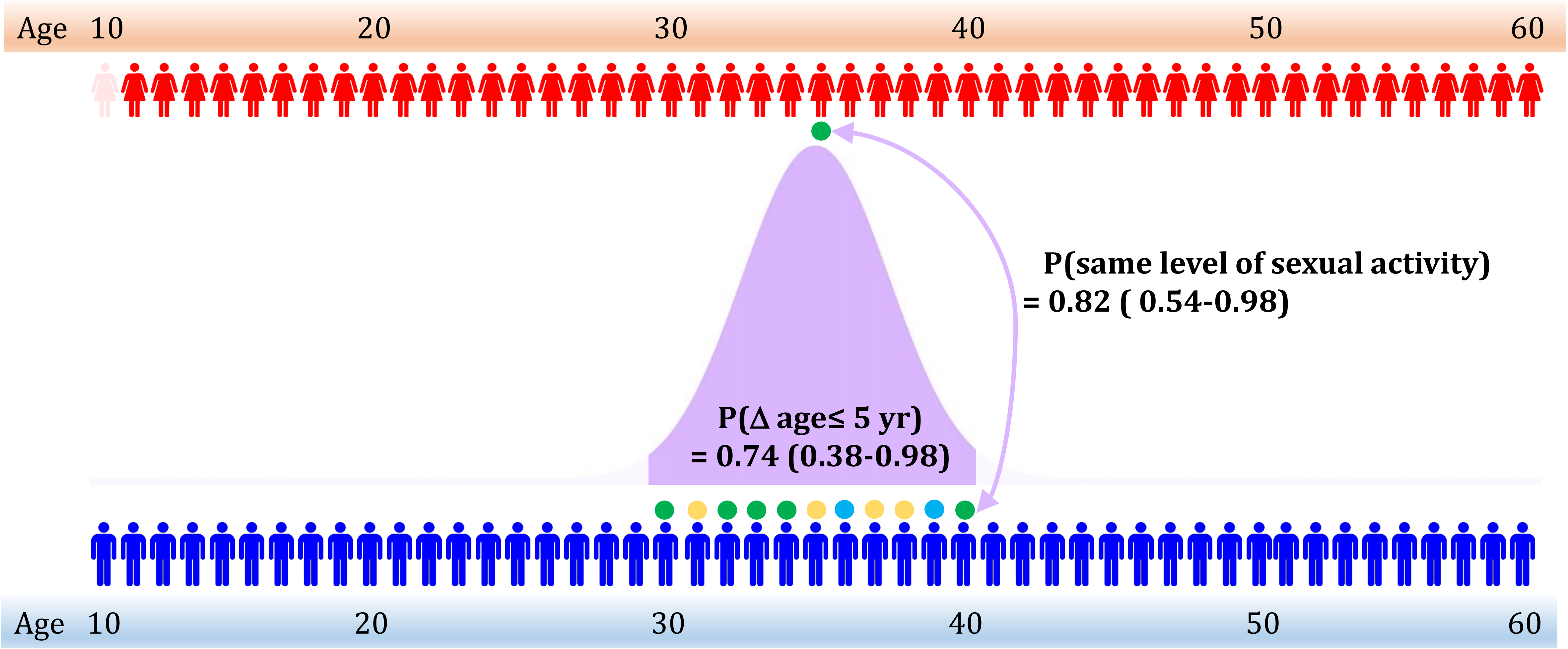
Data vs. fitted model



Inferred key parameters



Sexual mixing is highly assortative across age and sexual activity levels



Vaccination scenarios

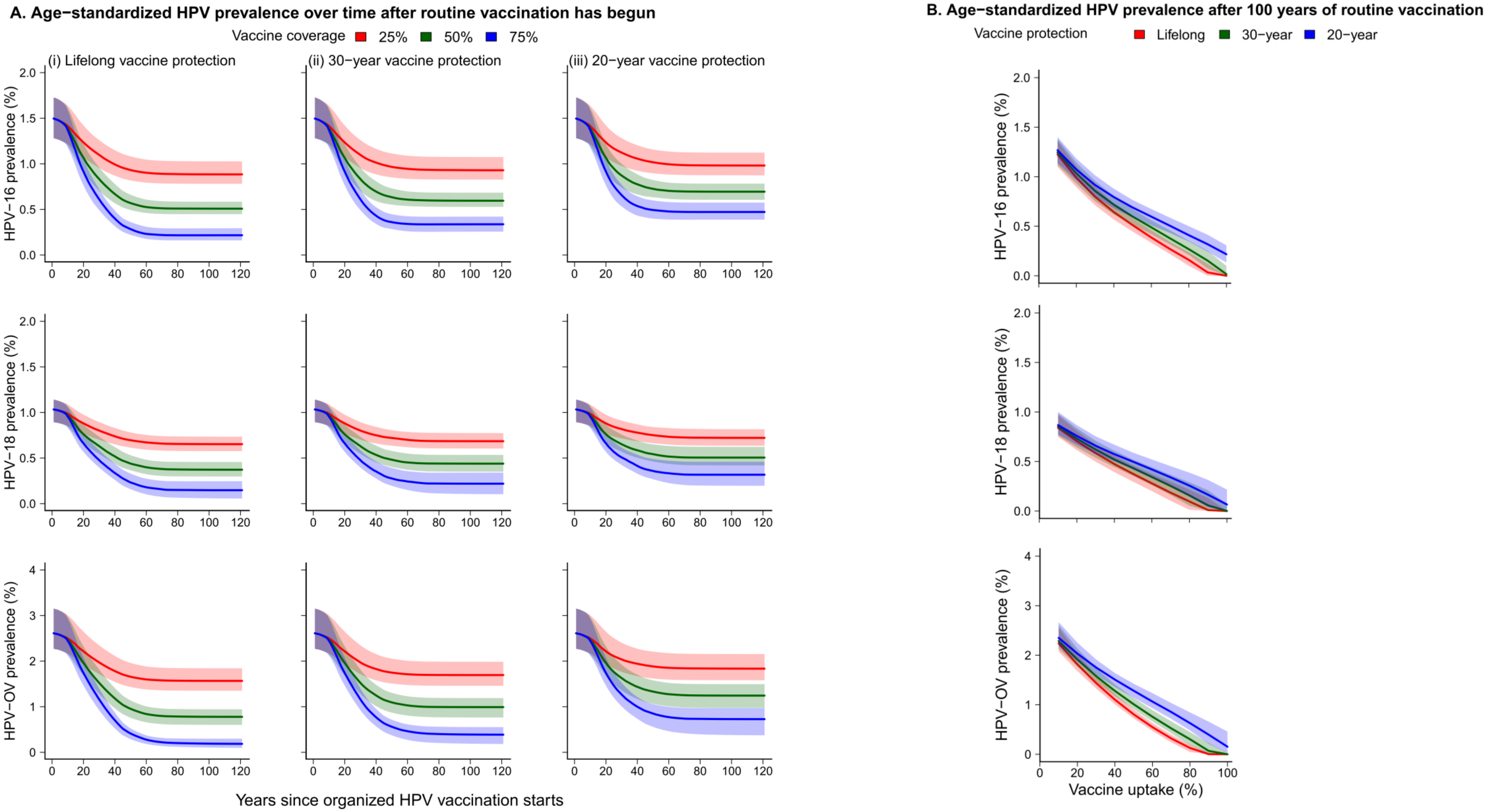
- Vaccine efficacy
  i. HPV-16: 95.5% (90%-98.4%)
  ii. HPV-18: 95.8% (84.1%-99.5%)
  iii. HPV-OV: 96% (94.4%-97.2%)

- Duration of vaccine protection: 20 years, 30 years and lifelong

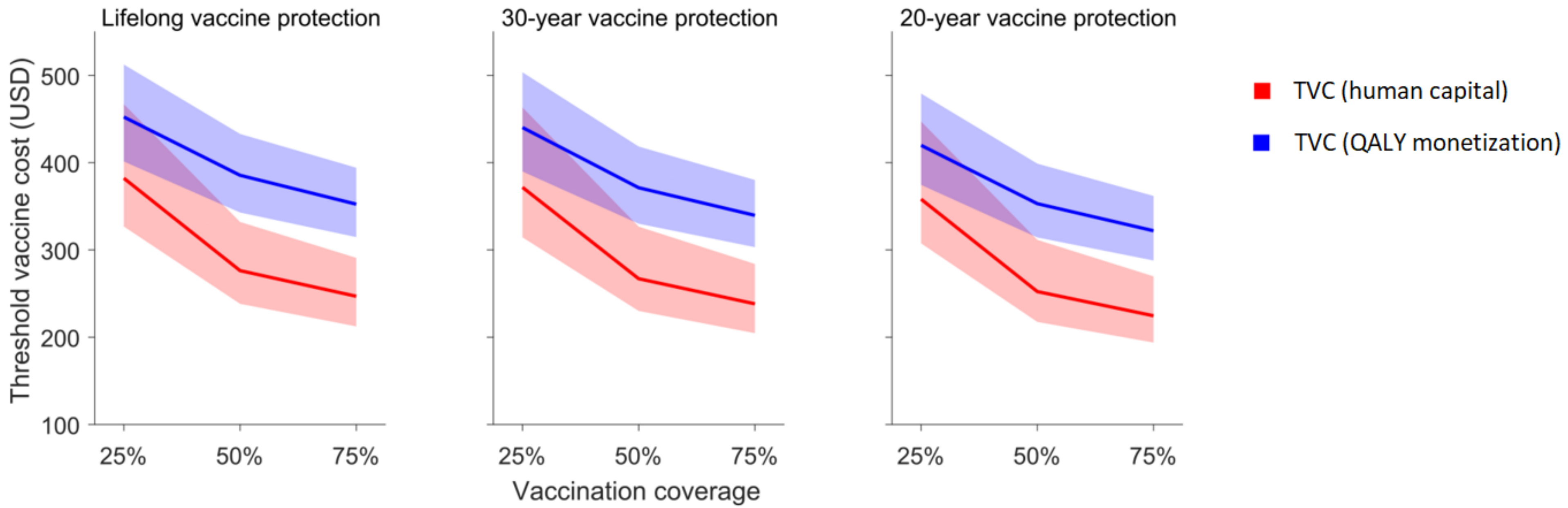
- Routine vaccine uptake: 25%, 50%, 75%
  - Our previous survey suggested that around 40-50% of mothers in Hong Kong would consent HPV vaccination for their adolescent daughters
  - UK and Australia have two of the world's highest routine HPV vaccination coverages at around 70-80%

- Catch-up uptake is half of routine uptake

Epidemiologic impact of routine HPV vaccination



Threshold vaccine cost (TVC)



1. TVC under the human capital approach is always lower than that under the QALY monetization approach.
2. TVC is lowest (i.e. most stringent) when the duration of vaccination protection is 20 years and vaccine uptake is 75%.
3. Routine vaccination is cost-beneficial in this worst-case scenario if the cost for fully immunizing one girl is below US$224 ($194-$270).
4. Adding 2 years of catch-up vaccination has little impact on TVC.

Limitations

1. We have not accounted for the health benefits of 9-valent HPV vaccine in reducing the burden of genital warts caused by HPV-6 and HPV-11
   - Data on age-specific incidence of genital warts are needed

2. We have assumed that the duration and transmissibility of HPV infection are the same for males and females.

3. We have not considered potential changes in cervical cancer screening patterns after routine HPV vaccination has begun.

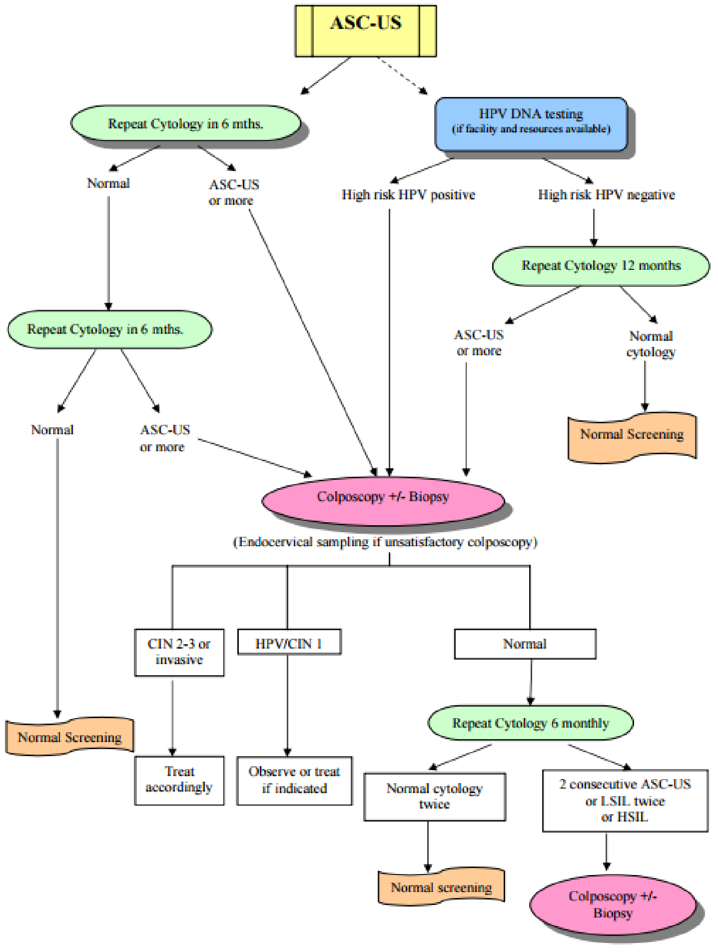
4. We have used only the human capital method in our CBA. Other CBA methods (e.g. those based on friction cost or the value of statistical life) may result in different cost-beneficial threshold vaccine costs.

Funding

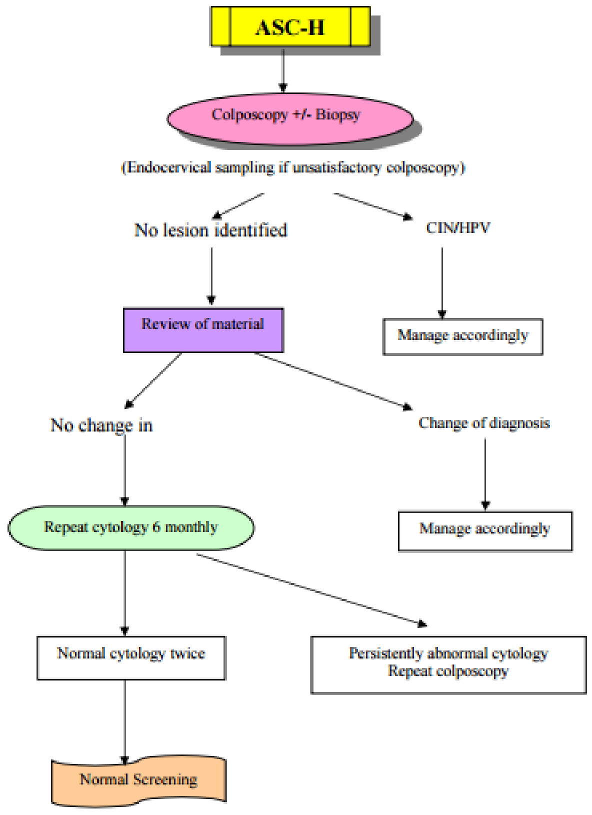
This work was partially supported by the Health and Medical Research Fund from the Food and Health Bureau, Hong Kong Special Administrative Region Government [Grant number: HKS-15-E04].

Cervical cancer screening is simulated based on the CSP recommendations where females with abnormal screening results are treated according to the management guidelines issued by the Hong Kong College of Obstetricians and Gynaecologists (HKCOG).

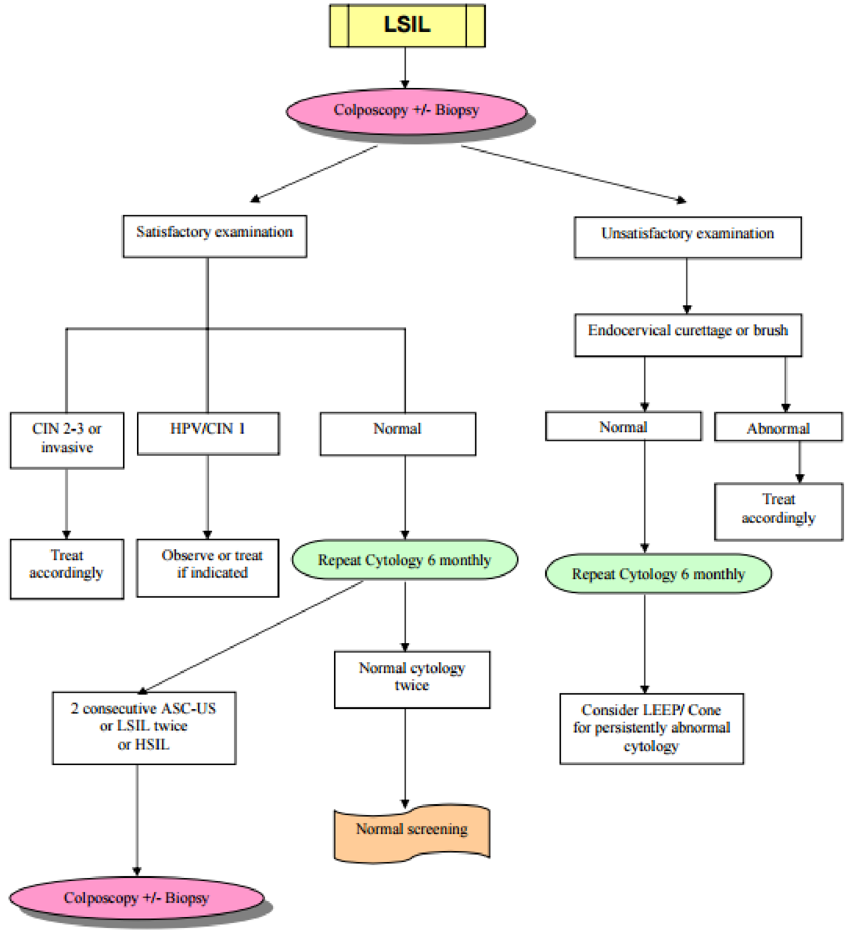
Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US)



Management of women with Atypical Squamous Cells-Cannot Exclude High grade SIL (ASC



Management of women with Low Grade Squamous Intraepithelial Lesion(LSIL)



Cost calculations

- Itemize the typical procedures performed for treating a given disease state
- Cost each procedure based on Hospital Authority Gazette No. 12/2013.
- Sum up the cost for each procedure.

Cost breakdown for local CeCx (Stage I)

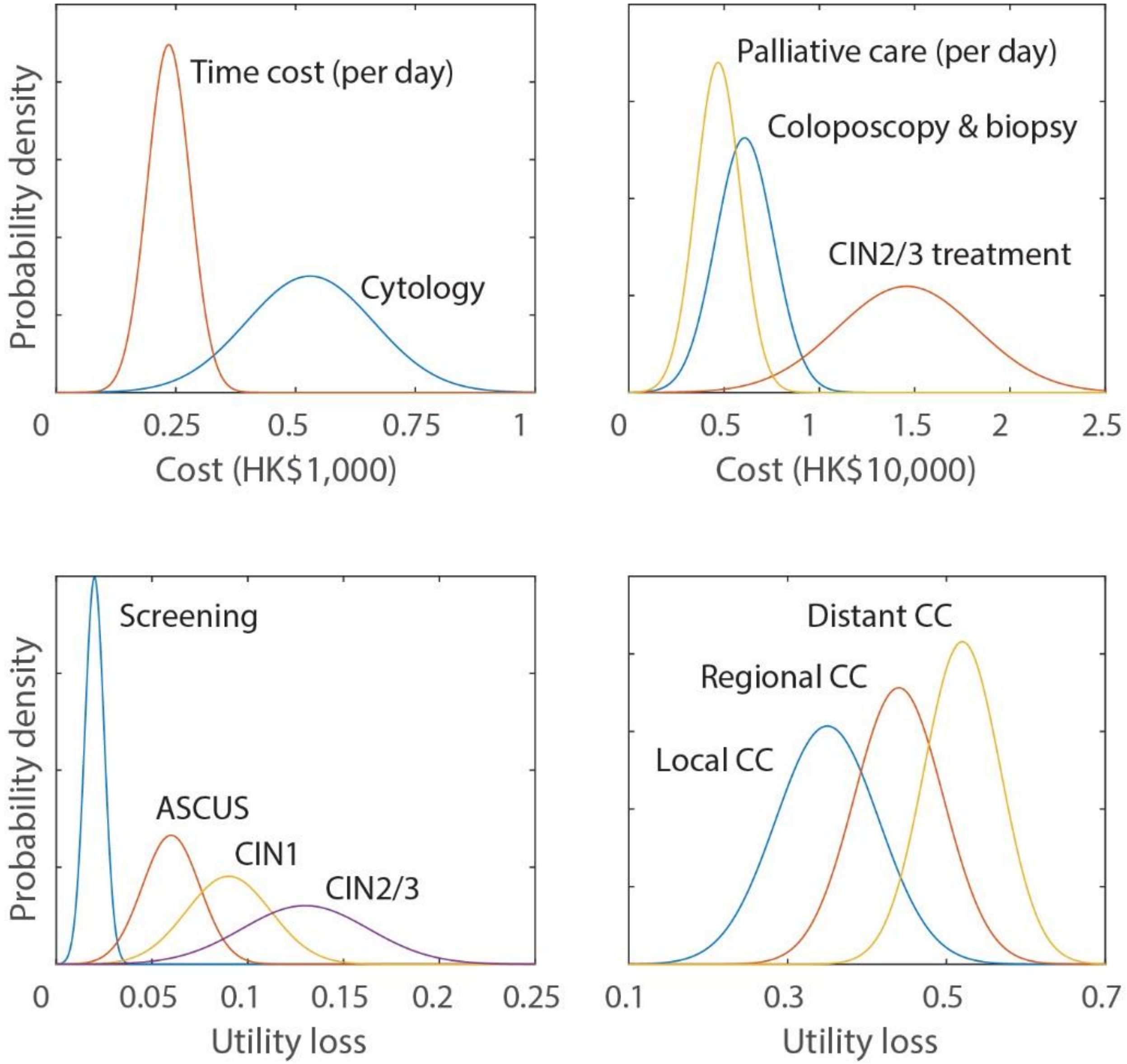
Items	Costs (HK$)
Wertheim's hysterectomy	83,450
Hospitalization (5 days, average)	5,640 / 3,760 (1st / 2nd class, daily)
Review of histopathology report	1,580
Total	108,530

Cost calculations

Cost breakdown for Regional CeCx (Stage II/III)

Items	Costs (HK$)
1. Radiotherapy	
- 3D / IMRT	89,640 / 157,310
2. Brachytherapy	110,960
- 4 sessions (2-day hospital)	
3. Chemotherapy, 6 cycles	1,326 x 6
- preparation for infusion	
- Cisplatin + Zofran (trigger nausea)	
Total	242,195

Cost and utility parameters



Coefficient of variation = 0.25
for most probability distributions

	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 1. 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.

We use the survey data published by the FPAHK to construct the sexual activity matrix 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.