香港中文大學
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香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Potential Cost-effectiveness of Herpes Zoster Vaccination for Older Adults in Hong Kong

Joyce H.S. YOU, PharmD, BCPS (AQ-Infectious Diseases)
School of Pharmacy
The Chinese University of Hong Kong

School of Pharmacy CUHK
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Project Team

Principal Applicant:
You, Hoi Sze Joyce
Associate Professor, School of Pharmacy,
The Chinese University of Hong Kong

Co-Applicants:
Chan, Kay Sheung Paul
Professor & Department Chairman Dept. of Microbiology,
The Chinese University of Hong Kong

Tsang, Tak Yin Owen
Consultant, Department of Medicine & Geriatrics,
Princess Margaret Hospital, Hospital Authority

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Mr. Law Tse-kwun Travis at Princess Margaret Hospital
Dr. Wai-kit Ming, School of Pharmacy, CUHK
Ms. Yu Wing-yin, School of Pharmacy, CUHK
Mr. Lee Chak-fai, School of Pharmacy, CUHK

Introduction

- **Varicella zoster virus causes herpes zoster (HZ) upon reactivation**
  - ➢ Patients who were previously infected in earlier stage of life
  - ➢ HZ manifestations: Severe pain and vesicles along the dermatome(s)
  - ➢ Post-herpetic neuralgia (PHN)
  - ➢ HZ incidence increases with age
  - ➢ Females are at higher risk than males

Introduction

- **HZ prevalence in Taiwan**
  - One-third of Chinese population developed HZ within their lifetime
    - 40-50 years old: 5.18 cases per 1000
    - >70 years old: 11.77 cases per 1000
- **Increasing size of aging population in Hong Kong**
  - Long life expectancies: >80 years for males and females
  - ≥50 years age groups accounted for 40% of the entire population
- **Females - 54% of seven million**
- **HZ prevalence in Hong Kong is anticipated to increase**

Introduction

- **Live-attenuated vaccine against HZ**
  - Reduced HZ cases (by 51%) and HPN cases (by 67%)
  - First approved in the US in 2006 for adults aged 60 years and older
  - Later approved in 2011 for adults aged 50 years and older
  - Vaccine efficacy against HZ in elderly aged ≥70 years (38%) significantly lower than the efficacy (70%) in the 50-59 year age group

Introduction

- **Adjuvanted HZ subunit vaccine (HZ/su) was approved in 2017 for adults aged 50 years**
  - Overall vaccine efficacy for adults aged 50 years and older: 97%
  - Efficacy for age groups 50-59, 60-69, 70-79 and ≥80 years: >90%
  - Advisory Committee on Immunization Practices (US) recommended HZ/su for healthy adults aged ≥50 years and for adults who had previously vaccinated with the live-attenuated HZ vaccine

Introduction/Aim

- **The Hong Kong adult vaccination program subsidized by government currently does not include zoster vaccine**
- **Universal varicella vaccination is included in children vaccination program subsidized by the Hong Kong government (2014)**
    - Possibly reduced the exogenous boosting effect in the community

Aim:

- To inform decision-making on the potential cost-effectiveness of herpes zoster vaccination for older adults in Hong Kong

Objectives

- To translate clinical and economic data into expected quality-adjusted life-years (QALYs) and costs for vaccination against HZ in various adult age and gender groups using Markov modelling

- To identify influential parameters on the expected QALYs and costs in each age and gender group for vaccination against HZ and related morbidity and mortality

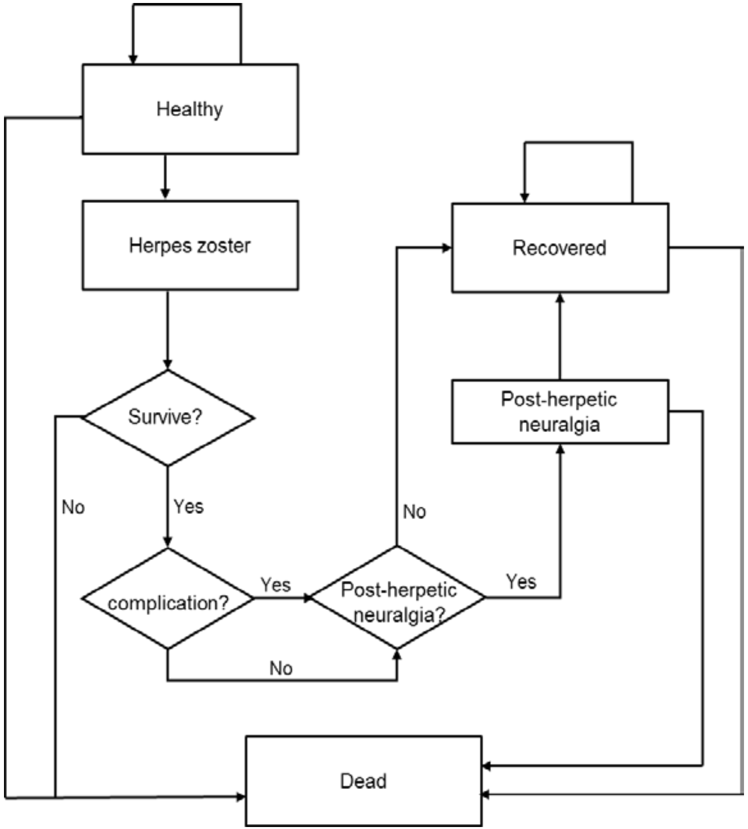
- To describe the acceptance per willingness-to-pay of zoster vaccination at different age and gender groups from societal perspective and healthcare provider's perspective

- To present the most reasonable and cost-effective vaccination strategy for Hong Kong from health economical point of view, based on the findings of objectives (1) to (3)

Methods—Model Design

- **Markov model design**
  - For a hypothetical cohort of immunocompetent older adults and with no contraindications for HZ/su
  - 50 years old at the entry of the model
  - Four vaccination strategies
    - Vaccination at entry of model (vaccination at age 50 years
    - Watchful waiting for next 10 years and vaccinated at age 60 years (defer vaccination to age 60 years)
    - Watchful waiting for next 20 years and vaccinated at age 70 years (defer vaccination to age 70 years)
    - No vaccination
  - From the perspectives of public healthcare providers and society

Methods—Model Design



- Vaccination might cause adverse events and require medical attention
- All hypothetical subjects might survive or die from all causes in each cycle
- Survived subjects might experience HZ and receive treatment in outpatient or inpatient setting
- Inpatients might develop complications (such as nervous system infection, ophthalmicus, Ramsay Hunt Syndrome, secondary skin and soft tissue infection (SSTI), disseminated HZ) and might die or survive
- Survived HZ patients might develop PHN, and the duration of PHN varied by age and gender

Methods—Clinical Inputs

- **Literature search on MEDLINE over the period 2000-present was performed**
  - using keywords "herpes zoster", "post-herpetic neuralgia", "neurologic complications", "meningitis", "ophthalmic complications", "herpes zoster vaccination", "adjuvanted herpes zoster subunit vaccine", "vaccine coverage", "vaccine safety", "outpatient care", "hospitalization", and "mortality"
- **The selection criteria of clinical trials**
  - Reports written in English, patients aged 18 years or above, incidence of events reported.
- **Preferred studies are meta-analyses or randomized controlled trials**

Methods—Clinical Inputs

	Base-case value		Range	Distribution
Vaccine uptake	Male	Female		
1st dose	100%	100%	0-100%	Uniform
2nd dose (among 1st dose receivers)	100%	100%	0-100%	Uniform
Duration of injection-site reaction (days)	2		1-3	Triangular
Serious adverse event within 30 days after vaccination	0%		0-0.1%	Uniform
Duration of serious reaction (days)	1.5		1-2	Triangular

Percentage of PHN i cases			
Age 50-59			
Age 60-79			
Age ≥80			
Monthly probabilities of persist: $P(t)=1-\exp[\lambda(t-1)^{\gamma}-\lambda t^{\gamma}]$			
Age <60			
Age ≥60			
Vaccine efficacy			
2-dose long-term waning function			
Efficacy function intercept	1.0765		
Annual waning rate	0.0319	0.0255-0.0383	Triangular
1-dose long-term waning function			
Efficacy function intercept	0.8801		
Annual waning rate	0.0507	0.0406-0.0608	Triangular

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Methods—Utility Inputs

Utility inputs	Base-case value		Range	Distribution
Age and gender specific utility	Male	Female	-	-
Age 50-54	0.92	0.92		
Age 55-64	0.92	0.84		
Age >65	0.84	0.84		
Utility decrements				Triangular
Vaccine injection site pain	0.01		0.005-0.015	
Serious reaction	0.5		0.4-0.6	
HZ at outpatient care	0.31		0.25-0.37	
HZ at inpatient care without complication	0.42		0.34-0.50	
HZ at inpatient care with complication	0.75		0.60-0.90	
PHN	0.42		0.31-0.75	

Methods—Cost Inputs

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Indirect costs	Base-case value		Range	Distribution
Labour force participation rate	Male (range)	Female (range)		Beta
Age 50-54	90.8% (76.6-100%)	66.0% (52.8-79.2%)		
Age 55-59	81.4% (65.1-97.7%)	50.2% (40.2-60.2%)		
Age 60-64	60.5% (48.4-72.6%)	29.2% (23.4-35.0%)		
Age ≥65	15.6% (12.5-18.7%)	4.8% (3.8-5.8%)		
Unemployment rate				Beta
Age 50-59	3.2% (2.6-3.8%)	2.8% (2.2-3.4%)		
Age ≥60	2.3% (1.8-2.8%)	2.0% (1.6-2.4%)		
Median monthly earning of employed persons (USD)				Triangular
Age 50-59	19000 (15200-22800)	12000 (9600-14400)		
Age ≥60	13000 (10400-15600)	8700 (6960-10440)		
Length of hospitalization (days)	Median		IQR	Triangular
Ophthalmicus	5		3-8	
Secondary skin and soft tissue infection	3		2-7	
Ramsay Hunt Syndrome	11		4-17	
Disseminated HZ	10		8-12	
Central nervous system infection	43		34-52	
No complication/PHN	5		3-8	
Number of clinic visit for outpatient HZ case (no complication/PHN)	1		1-2	

Methods

- **Cost-effectiveness Analysis**
  - Base-case expected costs, incidence of HZ and PHN and QALY loss were calculated assuming 100% vaccine coverage
  - Cost per HZ case avoided, cost per PHN avoided and cost per QALY saved were calculated
  - The benefit-cost ratio (BCR) was calculated
    - Benefit (savings) of a vaccination strategy defined as: Cost of HZ and PHN without vaccination – Cost of HZ and PHN with vaccination
  - Dominated option: more costly and gained less QALYs than comparator
  - A option was more costly and gained higher QALYs than comparator
    - Incremental cost per QALY saved (ICER) : Δcost/ΔQALYs

Methods

- **Cost-effectiveness Analysis**
  - Willingness-to-pay (WTP) threshold: 3× GDP per capita of Hong Kong
  - GDP per capita HKD339,500 in 2016
- **Sensitivity analysis**
  - One-way sensitivity analysis
    - Conducted over the upper and lower limits of the variables
  - Probabilistic sensitivity analysis
    - 10,000 Monte Carlo Simulations
    - 1st and 2nd dose vaccine uptake rates: 0-100%
    - Acceptability curves: showing the probability of each study arm to be accepted as the preferred option over zero to HKD1,018,500 (3× GDP per capita)

Methods

- **Scenario analysis**
  - Conducted to examine the impact of vaccine coverage and recurrent HZ
  - Vaccine coverage
    - Best-case scenario: 59.5% for the 1st dose and 100% for the 2nd dose
    - Worst-case scenario: 3.1% for 1st dose and 59.5% for 2nd dose
  - Recurrence rate of HZ
    - Similar incidences of HZ recurrence and first-episode HZ
    - Age-sex specific incidence of HZ used as one-time HZ recurrence therefore adopted

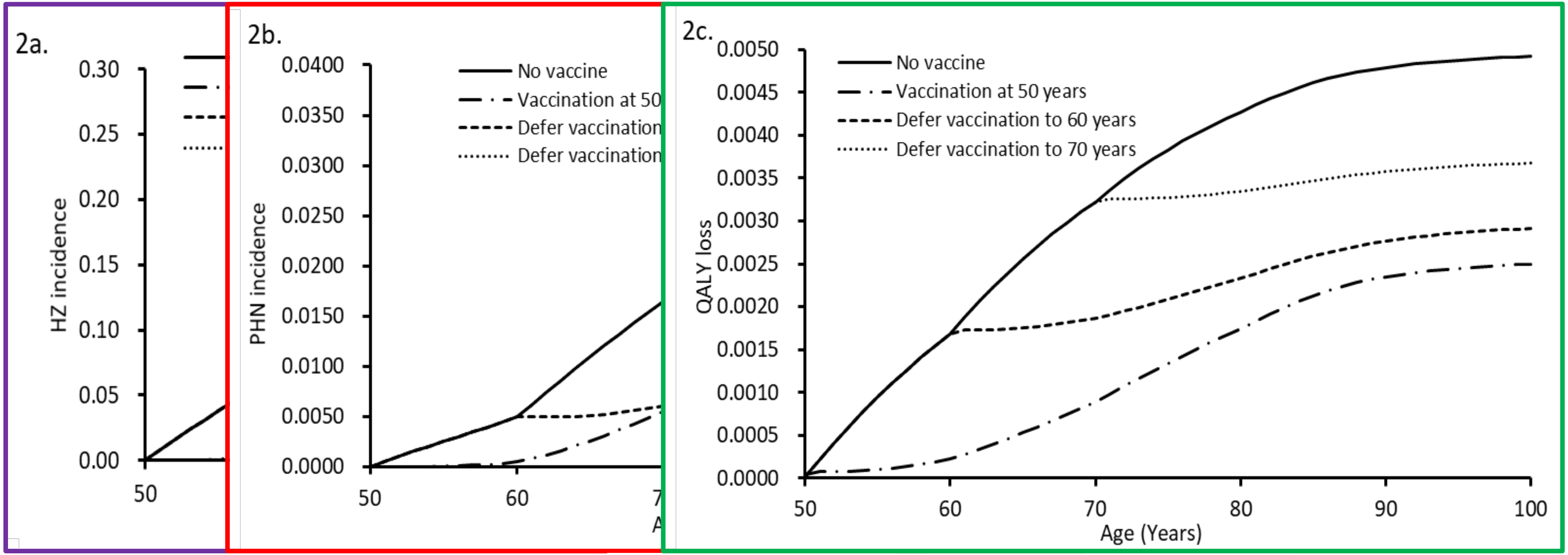
Results—Expected model outcomes in base-case analysis

Strategy		Direct costs (HKD)	Indirect costs (HKD)	Total cost (HKD)	HZ incidence	PHN incidence	QALY loss
No vaccination							
		565	36	601	**28.6**	3.86	0.00492
	Vaccine cost	0	0	0			
	HZ cost	565	36	601			
Defer vaccination to age 70 years							
		1081	36	1117	19.5	2.39	0.00368
	Vaccine cost	667	0	667			
	HZ cost	414	36	450			
Defer vaccination to age 60 years							
		1416	28	1444	16.5	2.19	0.00291
	Vaccine cost	1083	0	1083			
	HZ cost	333	28	361			
Vaccination at 50 years							
		1931	5	1936	16.6	2.80	0.00250
	Vaccine cost	1641	0	1641			
	HZ cost	290	5	295			

Results—Model validation

- In the arm of no vaccination, the expected life-long HZ incidence of 50 years old immunocompetent adults was **28.6%**.
- The lifetime risk of unvaccinated population having one occurrence of HZ in Taiwan was 32.2% (**30.2%** after adjusting for immunocompetent population).
- It was similar to the simulated life-long HZ risk and therefore supported the validity of present Markov model simulation of HZ incidence in unvaccinated immunocompetent adults.

Results—Change of (a) HZ incidence, (b) PHN incidence, (c) QALY loss over model time horizon (50 years)



HZ incidence PHN incidence QALY loss

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Results—Expected costs per HZ avoided, PHN avoided, QALY saved, benefit-cost ratio and ICER

Strategy	Cost per HZ avoided (HKD)	Cost per PHN avoided (HKD)	Cost per QALY saved[a]	Benefit-cost ratio[b]	ICER[c]
Defer vaccination to age 70 years	5,670	35,102	416,129	0.226	416,129
Defer vaccination to age 60 years	6,967	50,479	419,403	0.222	**424,675**
Vaccination at 50 years	11,125	125,943	551,653	0.186	1,200,000

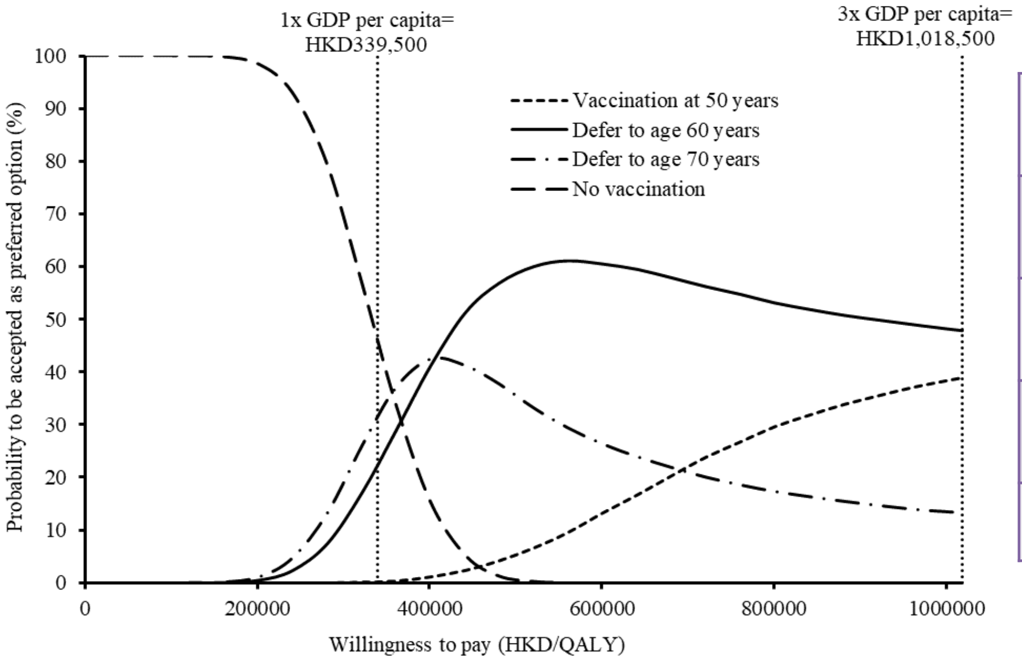
a: Cost per QALY saved versus no vaccination = (Total $\text{cost}_{\text{vaccine}}$ – Total $\text{cost}_{\text{no vaccine}}$)/(QALY $\text{loss}_{\text{no vaccine}}$ – QALY $\text{loss}_{\text{vaccine}}$)
b: Benefit of a vaccination strategy = Cost of HZ and PHN without vaccination – Cost of HZ and PHN with vaccination; Benefit-cost ratio= Benefit of vaccine/Cost of vaccine
c: ICER= (Total $\text{cost}_{\text{vaccine}}$ – Total $\text{cost}_{\text{next less costly option}}$)/(QALY $\text{loss}_{\text{next less costly option}}$ – QALY $\text{loss}_{\text{vaccine}}$); strategy with ICER less than HKD1,018,500 was considered as cost-effective

Results—One-way sensitivity analysis

- The base-case results (deferring vaccination to age 60 years to be cost-effective) was sensitive to 10 model inputs
- Vaccination at age 50 years became the preferred cost-effective option when any of these 10 model input values crossed the threshold

Influential factors	Base-case value	Threshold value
Utility value of HZ at outpatient care	0.31	>0.35
Annual waning rate of 2-dose HZ/su vaccination	0.0319	<0.0297
Direct cost per outpatient HZ case treatment (HKD)	2,413	>5,293
Direct cost per 2-dose vaccination (HKD)	1,625	<1,419
Annual HZ incidence per 1000 females aged 50-59 years	8.7	>10.1
Annual HZ incidence per 1000 males aged 50-59 years	6.7	>7.5
Vaccine uptake (1st dose) rate of females aged 60 years	100%	<90%
Vaccine uptake (1st dose) rate of males aged 60 years	100%	<87%
Vaccine uptake (2nd dose) rate of females aged 60 years	100%	<81%
Vaccine uptake (2nd dose) rate of males aged 60 years	100%	<74%

Results—Probabilistic sensitivity analysis



Strategy	1× GDP per capita	3× GDP per capita
Vaccination at 50 years	0.2%	38.9%
Vaccination at 60 years	22.4%	47.8%
Vaccination at 70 years	31.9%	13.3%
No vaccine	45.4%	0%

Results—3 Scenario analyses

Strategy	Total cost (HKD)	Incremental cost (HKD)[a]	QALY loss	QALY saved[b]	ICER (HKD/QALY)[c]
Base-case scenario: No recurrent HZ; 1st dose and 2nd dose VC 100% (vaccine approach)					
No vaccination	601	-	0.00492	-	
Defer vaccination to age 70 years	1,117	516	0.00368	0.00124	416,129
Defer vaccination to age 60 years	1,444	327	0.00291	0.00077	424,675
Vaccination at 50 years	1,936	492	0.00250	0.00041	1,200,000
Scenario 1: Recurrent HZ; 1st dose and 2nd dose VC 100% (vaccine approach)					
No vaccination	690	-	0.00565	-	-
Defer vaccination to age 70 years	1,191	501	0.00428	0.00137	365,693
Defer vaccination to age 60 years	1,493	302	0.00330	0.00098	308,163
Vaccination at 50 years	1,964	471	0.00273	0.00057	826,316

HZ=herpes zoster; VC=vaccine coverage

a: Incremental cost=Total $\text{cost}_{\text{vaccine}}$ – Total $\text{cost}_{\text{next less costly option}}$

b: QALY saved = QALY $\text{loss}_{\text{next less costly option}}$ – $\text{QALYloss}_{\text{vaccine}}$

c: ICER=(Total $\text{cost}_{\text{vaccine}}$ – Total $\text{cost}_{\text{next less costly option}}$)/(QALY $\text{loss}_{\text{next less costly option}}$ – $\text{QALYloss}_{\text{vaccine}}$)

Results—3 Scenario analysis

Strategy	Total cost (HKD)	Incremental cost (HKD)[a]	QALY loss	QALY saved[b]	ICER (HKD/QALY)[c]
Scenario 2: Recurrent HZ; 1st dose VC=59.5%; 2nd dose VC=100% (best-case policy approach)					
No vaccination	690	-	0.00565	-	
Defer vaccination to age 70 years	989	299	0.00484	0.00081	396,156
Defer vaccination to age 60 years	1,168	179	0.00425	0.00059	303,390
Vaccination at 50 years	1,447	279	0.00390	0.00035	797,143
Scenario 3: Recurrent HZ; 1st dose VC=3.1%; 2nd dose VC=59.5% (worse-case policy approach)					
No vaccination	690	-	0.00565	-	
Defer vaccination to age 70 years	703	13	0.00561	0.00004	325,000
Defer vaccination to age 60 years	710	7	0.00559	0.00002	350,000
Vaccination at 50 years	718	8	0.00555	0.00004	200,000

HZ=herpes zoster; VC=vaccine coverage

a: Incremental cost=Total cost$_{vaccine}$ – Total cost$_{next\ less\ costly\ option}$

b: QALY saved = QALY loss$_{next\ less\ costly\ option}$ – QALYloss$_{vaccine}$

c: ICER=(Total cost$_{vaccine}$ – Total cost$_{next\ less\ costly\ option}$)/(QALY loss$_{next\ less\ costly\ option}$ – QALYloss$_{vaccine}$)

Discussion

- **First HZ/su cost-effectiveness analysis for Chinese population**
  - ➢ Base-case results showed that all vaccination strategies saved QALYs at higher cost
  - ➢ Deferring vaccination to age 60 years was the acceptable cost-effective option at WTP= 3× GDP per capita (HKD1,018,500)
  - ➢ Probabilistic sensitivity analysis found deferring vaccination to age 60 years the most likely option (47.8%) to be cost-effective at WTP=3× GDP per capita

- **Cost-effectiveness analysis in German**
  - ➢ A Markov model with the cohort entering at 50 years and vaccinated at 60 years
  - ➢ The QALYs saved by deferring HZ live-attenuated vaccine to 60 years (0.00050 QALYs) lower than deferring HZ/su to 60 years (0.00201 QALYs) in the present study
  - ➢ Consistent with the clinical findings:
    - o High HZ/du vaccine efficacy (above 90%) despite vaccination age
    - o Lower vaccine efficacy (<50%) of live-attenuated vaccine at older age groups

Ultsch B, et al. Health economic evaluation of vaccination strategies for the prevention of herpes zoster and postherpetic neuralgia in Germany. BMC Health Serv Res. 2013;13:359

Discussion

- **Cost-effectiveness analysis for HZ/su and live-attenuated HZ vaccine in the US**
  - ➢ The acceptance of HZ/su to be cost-effective (at probability of 80%) occurring at higher WTP for younger age (60 years), similar to the present findings
  - ➢ ICERs (21,726-30,084 USD/QALY) of HZ/su strategies in the US < ICERs (416,129-1,200,000 HKD/QALY; USD1=HKD7.8) in the present study
    - o Much lower cost of HZ treatment in Hong Kong (HKD22,520 per inpatient case; HKD2413 per outpatient case) than the US (USD8656 per HZ hospitalization; USD412 per acute HZ cases)
    - o Vaccine cost assumed in the present study (HKD1625) similar to the vaccine cost (USD280) used in the US study
    - o The cost-saving from each HZ case avoided by vaccination was lower in Hong Kong comparing to the US and therefore had less impact to offset the vaccine cost.

Le P, Rothberg MB. Cost-effectiveness of the Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults. JAMA Intern Med. 2018;178(2):248-258.

Limitations

- Simulating the outcomes of vaccination with HZ/su using a model simplified real-life events of HZ
- The clinical and utility parameters of the model were estimated from findings outside Hong Kong and may affect the applicability of model results
- Despite that all model inputs were evaluated over a wide range of values in the sensitivity analysis to examine their influence on the robustness of model results, the selection of base-case values primarily affects the cost-effectiveness analysis results

Conclusions

- For healthy adults aged 50 years old, offering vaccination with HZ/su at aged 50 years, as well as deferring vaccination to age 60 years and to age 70 years appears to reduce HZ and PHN incidence and save QALYs at higher cost from the societal perspective of Hong Kong.

- The cost-effectiveness acceptance of each strategy is highly subject to WTP threshold per QALY saved. Deferring vaccination to age 60 years is more likely than vaccination at 50 years to be accepted as the cost-effective option over a broad range of WTP.

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SHORT COMMUNICATION

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Economic Analysis of Herpes Zoster in a Hospital Setting in Hong Kong

Wai-kit MING[1,2], Wing-yin YU[1], Owen Tak-yin TSANG[3], Paul Kay-sheung CHAN[4] and Joyce Hoi-sze YOU[1]

[1]School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, NT, Hong Kong, [2]Harvard Medical School, Harvard University, Boston, Massachusetts, USA, [3]Department of Medicine & Geriatrics, The Princess Margaret Hospital, Hospital Authority, and [4]Department of Microbiology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong. E-mail: joyceyou@cuhk.edu.hk

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RESEARCH ARTICLE

Optimal gender-specific age for cost-effective vaccination with adjuvanted herpes zoster subunit vaccine in Chinese adults

Joyce H. S. You[1]*, Wai-kit Ming[1,2], Owen Tak-yin Tsang[3], Paul Kay-sheung Chan[4]

1 School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China,
2 Harvard Medical School, Harvard University, Boston, Massachusetts, United States of America,
3 Department of Medicine & Geriatrics, The Princess Margaret Hospital, Hong Kong SAR, China,
4 Department of Microbiology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China

* joyceyou@cuhk.edu.hk

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Potential cost-effectiveness of adjuvanted herpes zoster subunit vaccine for older adults in Hong Kong

Joyce H.S. You[a,*], Wai-kit Ming[a,b], Chak-fei Lee[a], Owen Tak-yin Tsang[c], Paul Kay-sheung Chan[d]

[a] School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong
[b] Harvard Medical School, Harvard University, Boston, MA, USA
[c] Department of Medicine & Geriatrics, The Princess Margaret Hospital, Hospital Authority, Hong Kong
[d] Department of Microbiology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong