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Cost-effectiveness of annual trivalent inactivated influenza vaccine program by age and risk status

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ABSTRACT

Objective: To evaluate the cost-effectiveness of annual trivalent inactivated influenza vaccine (IIV3) under the context of Zhejiang province.

Methods: A state transition simulation model was constructed to estimate the health and economic outcomes of IIV3 vaccination program compared to no vaccination for hypothetical cohorts of Zhejiang province stratified by age and risk status. Model input parameters were chosen based on published literatures and expert advices. The analysis used societal perspectives and a one-year time horizon, and permanent outcomes were also included. The primary outcome was the incremental cost-effectiveness ratio (ICER), with expression of US dollars per quality adjusted life years (QALYs) gained.

Results: In subgroups not at high risk for influenza-related complications (non-high risk subgroup), ICER ranged from $6 268/QALY (for adults aged 50-64 years) to $11 260/QALY (for children aged from 6 months to 4 years). In subgroups at high risk for influenza-related complications (high risk subgroup), ICER ranged from cost-saving (adults aged ≥65 years) to $5 260/QALY (for children aged from 6 months to 4 years). ICER were most sensitive to changes in probability of influenza illness, cost of hospitalization, and probability of death for adults aged 18-49 years with non-high risk status.

Conclusions: ICERs of annual influenza vaccination varied by age and risk status but were less than the Gross Domestic Product (GDP) per capita of Zhejiang province ($17 745 in 2023), which remained cost-effective for all-age and different risk status groups from a societal perspective.

KEYWORDS: Influenza; Vaccination; Cost-effectiveness; Trivalent inactivated influenza vaccine; Risk

1. Introduction

Influenza circulates annually and causes substantial morbidity and mortality, with the highest burden in adults aged over 65 years and children under age of 5 years. Influenza caused 3-5 million severe cases and 290 000-650 000 deaths throughout the world annually[1,2]. Most of the influenza related deaths or hospitalizations occurred in senile population aged ≥65 years and children under 5 years old[3]. A meta-analysis from mainland China found the influenza-related outpatient visit rate ranged from 0.1 to 7.4 per

Summary

Question: Is the annual trivalent inactivated influenza vaccine (IIV3) vaccination strategy cost-effective in Zhejiang province?

Findings: In non-high risk subgroups, the incremental cost-effectiveness ratio (ICER) ranged from $6 268/QALY to $11 260/QALY. In high risk subgroups, ICER ranged from cost-saving to $5 260/QALY.

Meaning: These findings indicate ICERs of annual influenza vaccination varied by age and risk status but remained cost-effective for all-age and different risk status groups from a societal perspective.

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1 000 persons[4]. The influenza-related hospitalization rates were also higher among children and adolescents, with 384 per 100 000 children aged under the age of 5 years and 112 per 100 000 persons aged under 15 years[5]. The influenza-related all-age mortality was 23 per 100 000 persons and the mortality among adults aged ≥65 years was significantly higher than that for those aged <65 years[2].

Vaccine is one of most effective inters to prevent influenza. Almost one-third of the World Health Organization (WHO) Member States recommended influenza vaccination for the entire population or persons with high risk[6]. Influenza vaccination had been incorporated into the national immunization program (NIP) of many developed countries and some upper middle-income countries.

In mainland China, vaccination programs are categorized into NIP and non-NIP. The former are free of charge but mandatory, while the latter, including influenza vaccine, are self-funded and optional. Under the current self-paid policy, the coverage of influenza vaccination for all-age population is extremely low, remaining around 2%[7,8]. Chinese vaccine administration law, which was issued in 2019, recommended the gradual incorporation of self-funded vaccines into NIP. In the transitional period, local health authorities were encouraged to introduce new vaccines into the local immunization program and release the free-administration policy before NIP policy was initiated at national level. Currently, Zhejiang province provides the trivalent inactivated influenza vaccine (IIV3) to adults aged over 70 years and it could significantly improve the vaccination coverage from 2% to 37%. A government-funded influenza vaccination policy could not only reduce the disease burden by improving vaccination coverage, but also would improve public trust in vaccination[9,10].

Since the 2009 pandemic influenza A (H1N1) virus circulated as one of the seasonal influenza viruses, the epidemiologic characteristic of seasonal influenza had been changed[1,11]. Prior to 2009, influenza A/H3 predominant seasons were associated with more severe influenza-related health outcomes, but a recent epidemiologic study on influenza observed higher incidence of influenza illness in working-age adults[12]. Moreover, the surveillance data suggested that younger working-age adults now experience more severe influenza related illness during influenza A/H1 predominant seasons rather than influenza A/H3 predominant seasons[13]. Since the 2009 H1N1 strain is now circulating as part of the set of seasonal influenza viruses, the pattern of vaccine-averted influenza events across age and risk strata may differ.

Since 2010, the Advisory Committee on Immunization Practices (ACIP) implemented a universal influenza vaccination recommendation for all persons aged over 6 months and encouraged the use of more convenient settings to improve the coverage and reduce the cost[14]. Given the changes in recommendations from the latest Chinese vaccine administration law and the changes in the epidemiology of influenza, many public health authorities and experts proposed that the influenza vaccine should be included into NIP, providing free vaccination for all-age group aged ≥6 months. Importantly, a cost-effectiveness evaluation is needed to help decision-makers to develop the influenza vaccination strategy adapted to the local situation. Policy decisions at various levels are driven by the uncertainties of disease burden, the unclear picture of demographic structure and socioeconomic level. Hence, the objective of this study was to evaluate the health and economic outcomes related to annual IIV3 program for population aged ≥6 months by age and risk status based on the new evidence and under the context of Zhejiang province.

2. Methods

2.1. Study design

The state-transition simulation model was applied to assessing the health and economic outcomes for annul influenza vaccination. The hypothetical cohorts used in this study were constructed based on the 7th national census data (2020), which could reflect the differences in the influenza epidemiologic characteristics and vaccine effectiveness and would accurately estimate the cost-effectiveness of vaccination among different cohorts. Specifically, the general population were stratified by age as follow: 6 months-4 years, 5-17 years, 18-49 years, 50-64 years and ≤65 years in order to fit the census data we collected). Each cohort (age group) was further stratified by risk status as defined by China Center for Disease Control and Prevention (CDC): those at higher risk for influenza-related complications (‘high risk’) or not (‘non-high-risk’) [15]. Besides, cohort aged ≥65 years were all assumed as high risk for influenza-related complications. Finally, there were 9 separate subgroups for the data analysis. The time horizon was set to one year as most influenza cases and complications occurred within a single influenza season (6 months). Permanent outcomes, such as death and sequela following influenza-related hospitalization, were included for the duration of a lifetime. This study was performed from a societal perspective and all model input parameters were derived from published sources, supplemented by expert advices where data were scarce. The model was programmed using TreeAge Pro 2019 software.

2.2. Model construction

Figure 1 represented the simulation model, including influenza- and vaccination- related health states. During a given year, a person could experience uncomplicated influenza, influenza-related outpatient visit, influenza-related hospitalization, influenza-related death or no influenza-related health event. For those with an influenza-related

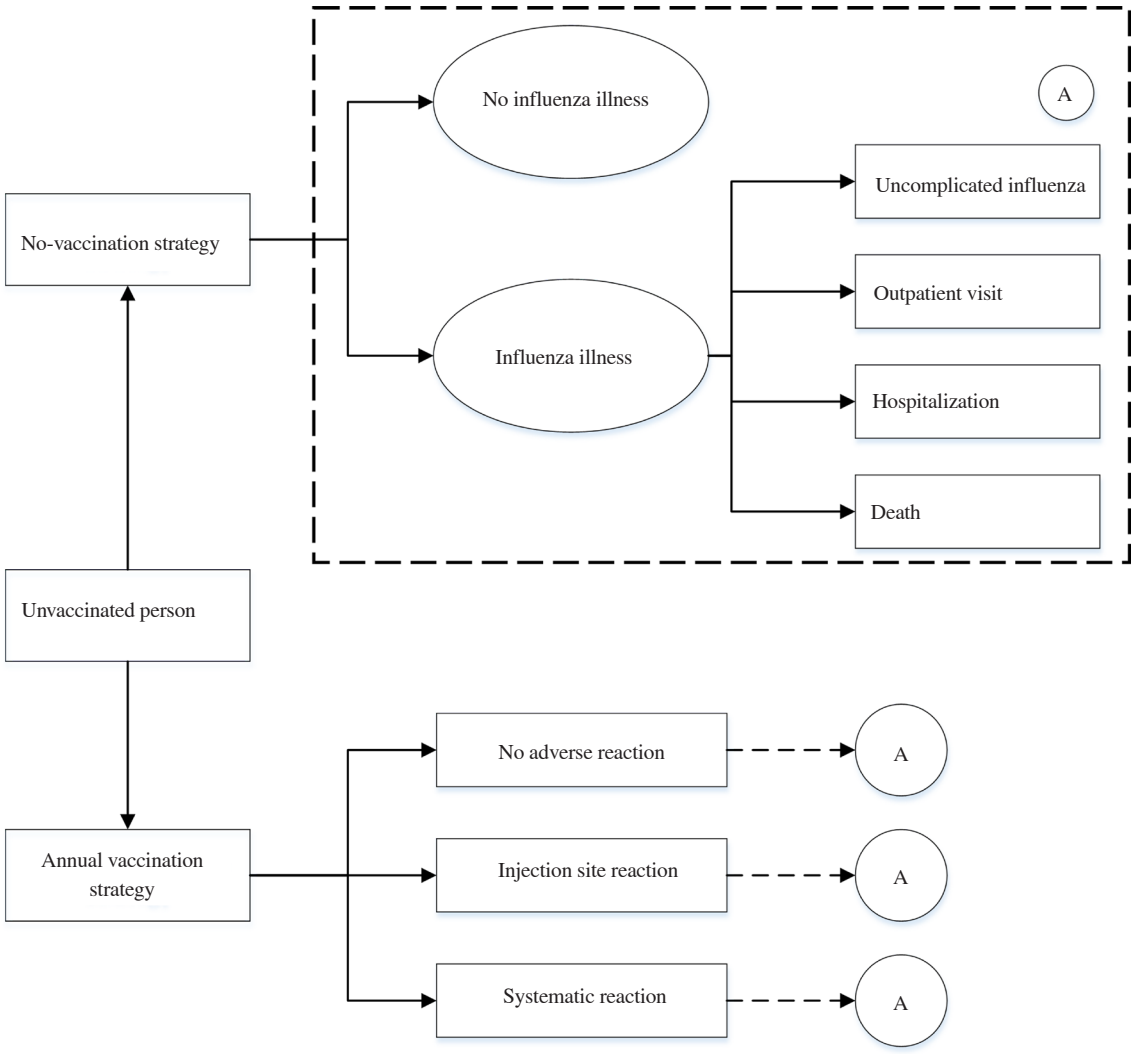

Figure 1. Annul influenza vaccination cost-effectiveness simulation model.

hospitalization, some would also experience sequelae associated with influenza. For person been vaccinated, vaccination-related adverse reactions, like injection site reaction and systematic reaction were also included.

The vaccination strategy in the model was providing a free IIV3 dosage for all persons aged ≥6 months. The vaccination program strategy was defined as vaccination with any kind of IIV3 available on the market and there might be more than ten influenza vaccine manufactures in mainland China. Other types of influenza vaccine rather than IIV3, such as quadrivalent inactivated influenza vaccine and trivalent live attenuated influenza vaccine, were not considered into our analysis for two reasons. First, there had been no confirmed detections of circulating B/Yamagata lineage viruses since March 2020 globally. Second, the trivalent live attenuated influenza vaccine was only applied for use among individuals aged 3-17 years, not for the all-age population.

2.3. Parameters

Influenza-related outcomes included episodes of influenza illness (outpatient visit or not), influenza-related hospitalization (with and without sequelae), and influenza-related death. We assumed that the incidence of influenza illness would not vary with risk status while the probability of complications following influenza would vary by risk status. This hypothesis was made due to insufficient evidence and we wanted to make a conservative approach to the results. Incidence of influenza illness, outpatient visits, hospitalizations, and death by both age were derived from published data from 2017-2018 influenza seasons[16]. The incidence of outpatient visits by risk status were estimated based on the proportion of high-risk and non-high risk persons reporting care-seeking studies[17]. The incidence of hospitalization and death by risk status were derived from a study using the proportion of influenza confirmed hospitalizations with at least one high-risk condition[18]. The probability of influenza-

related sequelae was based on a study on influenza-related neurological complications[19]. As the IIV3 available on mainland China were made by different manufactures, we assumed to choose an average vaccine effectiveness for all influenza vaccine types and for different age groups, which was derived from the US Flu Vaccine Effectiveness Network[20]. Vaccination-related adverse events were also assumed to be similar across all vaccine types from different manufactures, including episodes of injection site reactions and systematic reactions. A very small proportion of vaccinee was assumed to die or experience sequelae after vaccination. The incidence of adverse reactions was extracted from published reports[21-24] (Table 1).

Table 1. Probability parameters in the model.

Variable	Level	Base case	Range	Data distribution	Source
Probability of influenza	6 m-4 y	0.13	0.04-0.26	Beta	[16]
	5-17 y	0.10	0.03-0.19		
	18-49 y	0.07	0.02-0.14		
	50-64 y	0.13	0.02-0.31		
	≥65 y	0.08	0.00-0.21		
Probability of outpatient visit following influenza	NHR:			Beta	[16,17]
	6 m-4 y	0.66	0.64-0.69		
	5-17 y	0.51	0.49-0.53		
	18-49 y	0.36	0.34-0.37		
	50-64 y	0.40	0.38-0.42		
	HR:				
	6 m-4 y	0.78	0.75-0.80		
	5-17 y	0.60	0.57-0.62		
	18-49 y	0.45	0.43-0.48		
	50-64 y	0.49	0.47-0.52		
	≥65 y	0.56	0.54-0.58		
Incidence of hospitalization following influenza (/10 000 population)	NHR:			Beta	[16,18]
	6 m-4 y	5.21	1.49-11.18		
	5-17 y	1.51	0.22-1.68		
	18-49 y	1.27	0.19-1.39		
	50-64 y	10.18	4.28-12.08		
	HR:				
	6 m-4 y	62.74	18.04-134.56		
	5-17 y	16.54	4.75-35.51		
	18-49 y	22.81	6.55-48.94		
	50-64 y	41.85	7.25-104.62		
	≥65 y	75.53	10.27-205.18		
Incidence of death following influenza (/10 000 population)	NHR:			Beta	[16,18]
	6 m-4 y	0.05	0.00-0.25		
	5-17 y	0.02	0.00-0.14		
	18-49 y	0.03	0.00-0.12		
	50-64 y	0.10	0.01-0.29		
	HR:				
	6 m-4 y	0.64	0.00-2.99		
	5-17 y	0.37	0.00-2.91		
	18-49 y	1.00	0.09-4.91		
	50-64 y	2.49	0.34-7.51		
	≥65 y	8.32	1.09-23.47		
Probability of sequela following influenza-related hospitalization	-	0.01	0.00-0.02	Beta	[19]
Vaccine effectiveness	6 m-4 y	0.46	0.37-0.53	Beta	[20]
	5-17 y	0.43	0.28-0.54		
	18-49 y	0.35	0.24-0.45		
	50-64 y	0.40	0.24-0.53		
	≥65y	0.27	0.15-0.36		
Probability of injection site reaction following influenza vaccination	6 m-4 y	0.008	0.002-0.017	Beta	[21-24]
	5-17y	0.001	0.000-0.002		
	>18 y	0.011	0.000-0.044		
Probability of systematic reaction following influenza vaccination	6 m-4 y	0.013	0.001-0.025	Beta	[21-24]
	5-17 y	0.004	0.000-0.008		
	>18 y	0.011	0.000-0.044		
Probability of death following influenza vaccination(/10 000 doses)	-	0.01	Base ± 20%	Beta	[21-24]
Probability of sequelae following influenza vaccination(/10 000 doses)	-	0.000 1	Base ± 20%	Beta	[21-24]
Discount rate	-	0.03	0.02-0.05	Uniform	-

NHR: non-high risk for influenza-related complications; HR: high risk for influenza-related complications; Base case: base input value of parameters; m: months, y: years.

Cost estimates included direct medical, direct non-medical, and opportunity costs. The cost of self-medication for influenza was derived from a survey conduted in Jiangsu Province, China[25]. The cost of outpatient and hospitalizations were based on a national survey[26]. The cost of sequelae following influenza vaccination or influenza hospitalization was obtained from a previous study[27]. Vaccination costs included direct vaccine dose cost, administration service costs, syringe cost, which were derived from a national survey[28]. Children aged 6-35 months were given 2 doses of influenza vaccine as recommended China CDC. The cost due to adverse reactions following IIV3 vaccination was obtained from a published study[29]. The productivity loss was calculated by multiplying the time loss due to influenza illness by the average daily productivity in 2023 in Zhejiang province, only for individual aged 18-59 years. Where appropriate, unit costs were converted into US dollars ($1=CNY7.10, 2024). All costs and utility were adjusted to 2024 values by using the discount rate of 3% (Table 2).

The health utility was assessed by the quality-adjusted life years (QALYs), which were the main measure of health benefits. Health states in the model were primarily temporary except for sequelae or death. Each temporary health state would cause a loss in QALYs that was subtracted from the total QALYs, and the total QALYs were estimated through the discounted life expectancy for every subgroup. The utility weight associated with each health state and the duration of influenza illness were derived from an EQ-5D survey and a trade-off survey of US adults[30,31]. QALYs loss for each health state were calculated by multiplying the utility weight for the health state by the duration of the health state. For example, QALYs loss for permanent sequelae were calculated by multiplying the relevant utility weight by the remaining life expectancy (Table 3).

Table 2. Cost parameters in the model.

Variable	Base case	Range	Distribution	Source
OTC medications for minor influenza	$5.81	$4.01-6.69	Lognormal	[25]
Outpatient visit for influenza	$137.04	Base±20%	Lognormal	[26]
Hospitalization for influenza	$1 384.79	Base±20%	Lognormal	[26]
Sequelae following influenza-related hospitalization	$749 958	$0-1 543 176	Lognormal	[27]
Influenza vaccine price/dose	$2.82	Base±20%	Lognormal	[28]
Syringe price/dose	$0.17	Base±20%	Lognormal	[28]
Service cost/dose	$3.72	Base±20%	Lognormal	[28]
Physician visit for injection site reaction following influenza vaccination	$290	Base±20%	Lognormal	[29]
Physician visit for systematic reaction following influenza vaccination	$293	Base±20%	Lognormal	[29]
Cost for sequelae following influenza vaccination	$749 958	Base±20%	Lognormal	[27]
Productivity losses for non-medically attended influenza*	0.5 d	-	-	[30]
Productivity losses for medically attended influenza*	2.5 d	-	-	[30]
Productivity losses for influenza-related hospitalization*	3.8 d	-	-	[30]
Productivity losses for systematic reaction following influenza vaccination*	0.5 d	-	-	[30]
Daily productivity*	$52.25	-	-	Local data

*: Productivity losses parameters only for individuals aged 18-59 years; OTC: over the counter; NHR: non-high risk influenza-related complications; HR: high risk influenza-related complications; Base case: base input value of parameters. $: US dollars.

Table 3. Quality parameters in the model.

Variable	Level	Base case	Range	Age weights	Duration	Distribution	Source
Utility decrement for influenza illness	6 m-4 y	-	-	4.7×	7 d	Normal	[30,31]
	5-17 y	-	-	3.0×			
	18-49 y	0.008	0.008-0.009	-			
	50-64 y	-	-	0.9×			
	≥65 y	-	-	2.6×			
Utility decrement for hospitalization	6 m-4 y	-	-	2.2×	11.8 d	Normal	[30,31]
	5-17 y	-	-	1.7×			
	18-49 y	0.017	0.015-0.018				
	50-64 y	-	-	1.0×			
	≥65 y	-	-	1.5×			
Utility decrement for systematic reaction following influenza vaccination	-	0.001 2	0.001-0.002	-	3 d	Normal	[30]
Utility for sequelae	-	0.019 8	0.018-0.022	-	-	-	[30,31]
Utility for death	-	0	-	-	-	-	[30]
Life expectancy	6 m-4 y	77.52 y	-	-	-	-	Local data
	5-17 y	68.67 y	-	-	-	-	
	18-49 y	49.37 y	-	-	-	-	
	50-64 y	27.12 y	-	-	-	-	
	≥65 y	13.51 y	-	-	-	-	

Base case: base input value of parameters; d: days; m: months, y: years; -: data not avaliable.

2.4. Data analysis

The primary outcome was the incremental cost-effectiveness ratio (ICER), calculated by dividing the discounted net costs by discounted net QALYs. Secondary outcomes included the number of influenza cases averted, hospitalizations averted, deaths averted, adverse reactions occurred, QALYs gained, and net costs. The base-case analysis compared the vaccination program strategy to no vaccination using the societal perspective. The averted cases, hospitalizations, deaths were defined as the numbers of cases, hospitalization and deaths reduced under the IIV3 vaccination strategy, compared to the no-vaccination. One-way sensitivity analyses were conducted for most parameters among cohort aged 18-49 years by different risk status, in which each parameter value was changed over a plausible range to determine the impact from each parameter on the ICER. The plausible ranges were estimated by using 95% confidence intervals (*CI*) from relevant studies or ± 20% of base values if the *CI* was not available. Probabilistic sensitivity analysis (PSA) was also implemented to assess the effects of parameter uncertainty by defining parameters using a distribution of possible values and running the model for 10 000 iterations to get the 95% *CI* ranges.

3. Results

3.1. Base–case analysis

The results of base-case analysis were summarized in Table 4. The number of influenza cases averted compared to no vaccination varied by age, and it was the highest among children aged 6 months-4 years. We did not change the avert case number by risk status as we assumed the probability of getting influenza illness was the same under different risk status. On the other hand, the number averted hospitalization and death varied with age group and risk status. Hospitalizations averted were highest among children aged from 6 months to 4 years (2.89 hospitalizations averted per 1 000 vaccinated), followed by senile persons aged ≥65 yeas (2.04 hospitalizations averted per 1 000 vaccinated). The number of averted deaths were highest for older persons aged ≥65 years, with 0.22 deaths averted per 1 000 vaccinated.

The incidence of adverse reactions related to influenza vaccine was highest among children aged from 6 months to 4 years, with 21 adverse reactions occurred per 1 000 vaccinated. The incidence remained the same under different risk status as we assumed its probability was the same.

Based on 1 000 persons being vaccinated, annual influenza vaccination strategy was to be cost-saving for older persons aged ≥65 years with high-risk status. The net cost of annual influenza vaccination for other subgroups ranged from $2 207 per 1 000 vaccinated for adults aged 50-64 years to $11 260 per 1 000 vaccinated for children aged from 6 months to 4 years (Table 5).

Annual influenza vaccination could yield net positive QALYs for all subgroups, indicating health benefits of vaccination exceeded the risk of adverse reactions related to vaccine. The net QALYs gained were highest for children aged from 6 months to 4 years with high risk status (4.1 QALYs per 1 000 vaccinated), followed by older persons aged ≥65 years with high-risk status (3.9 QALYs per 1 000

Table 4. Projected net costs health benefits and risks of influenza vaccination by age and risk status (per 1 000 vaccinated).

Risk group	Age group	Net cost (US dollars)	QALYs gained	Cases averted	Hospitalizations averted	Deaths averted	Adverse events incurred
Non-high risk	6 m-4 y	11 260	2.5	60	0.29	0.002	21
	5-17 y	10 205	2.0	42	0.07	0.002	8
	18-49 y	9 705	2.0	25	0.05	0.001	11
	50-64 y	6 268	0.5	52	0.41	0.006	11
High risk	6 m-4 y	5 260	4.1	60	2.89	0.030	21
	5-17 y	5 103	3.8	42	0.71	0.020	8
	18-49 y	4 385	3.6	25	0.80	0.040	11
	50-64 y	2 207	2.9	52	1.68	0.100	11
	≥65 y	-904	3.9	21	2.04	0.220	11

Notes: The averted cases, hospitalizations, deaths were defined as the numbers of cases, hospitalization and deaths reduced under the IIV3 vaccination strategy, compared to the no-vaccination; m: months, y: years.

Table 5. Incremental cost-effectiveness ratios by age and risk status.

Risk group	Age group	US dollars/QALY gained	US dollars/Cases averted	US dollars/ Hospitalizations averted	US dollars/ Deaths averted
Non-high risk	6 m-4 y	11 260	4 504	187.67	38 828
	5-17 y	10 205	5 103	242.98	145 786
	18-49 y	9 705	4 853	388.20	194 100
	50-64 y	6 268	12 536	120.54	15 288
High risk	6 m-4 y	5 260	1 283	87.67	1 820
	5-17 y	5 103	1 343	121.50	7 187
	18-49 y	4 385	1 218	175.40	5 481
	50-64 y	2 207	761	42.44	1 314
	≥65 y	-904	-232	-43.05	-443

Notes: The averted cases, hospitalizations, deaths were defined as the numbers of cases, hospitalization and deaths reduced under the IIV3 vaccination strategy, compared to the no-vaccination; m: months, y: years.

vaccinated) as shown in Table 4.

Table 5 indicated the ICER of annual influenza vaccination varied by age and risk status. In non-high risk subgroups, the ICER ranged from $6 268/QALY (adults aged 50-64 years) to $11 260/QALY (children aged from 6 months to 4 years), and was most favorable for adults aged 50-64 years ($6 268/QALY). In high risk subgroups, influenza vaccination was cost-saving (ICER <0) for adults aged ≥65 years. For the remaining high-risk subgroups, influenza vaccination yielded ICERs that ranged from $2 207/QALY (adults aged 50-64 years) to $5 260/QALY (children aged from 6 months to 4 years).

3.2. Sensitivity analyses

In one-way sensitivity analyses, the ICERs for influenza vaccination were most sensitive to changes in probability of influenza illness, vaccine effectiveness, probability of systematic reactions for adults aged 18-49 years with non-high risk status, while were most sensitive to changes in probability of influenza illness, cost of hospitalization, probability of death for adults aged 18-49 years with high risk status (Figure 2).

Cost-effectiveness acceptability curves were depicted using

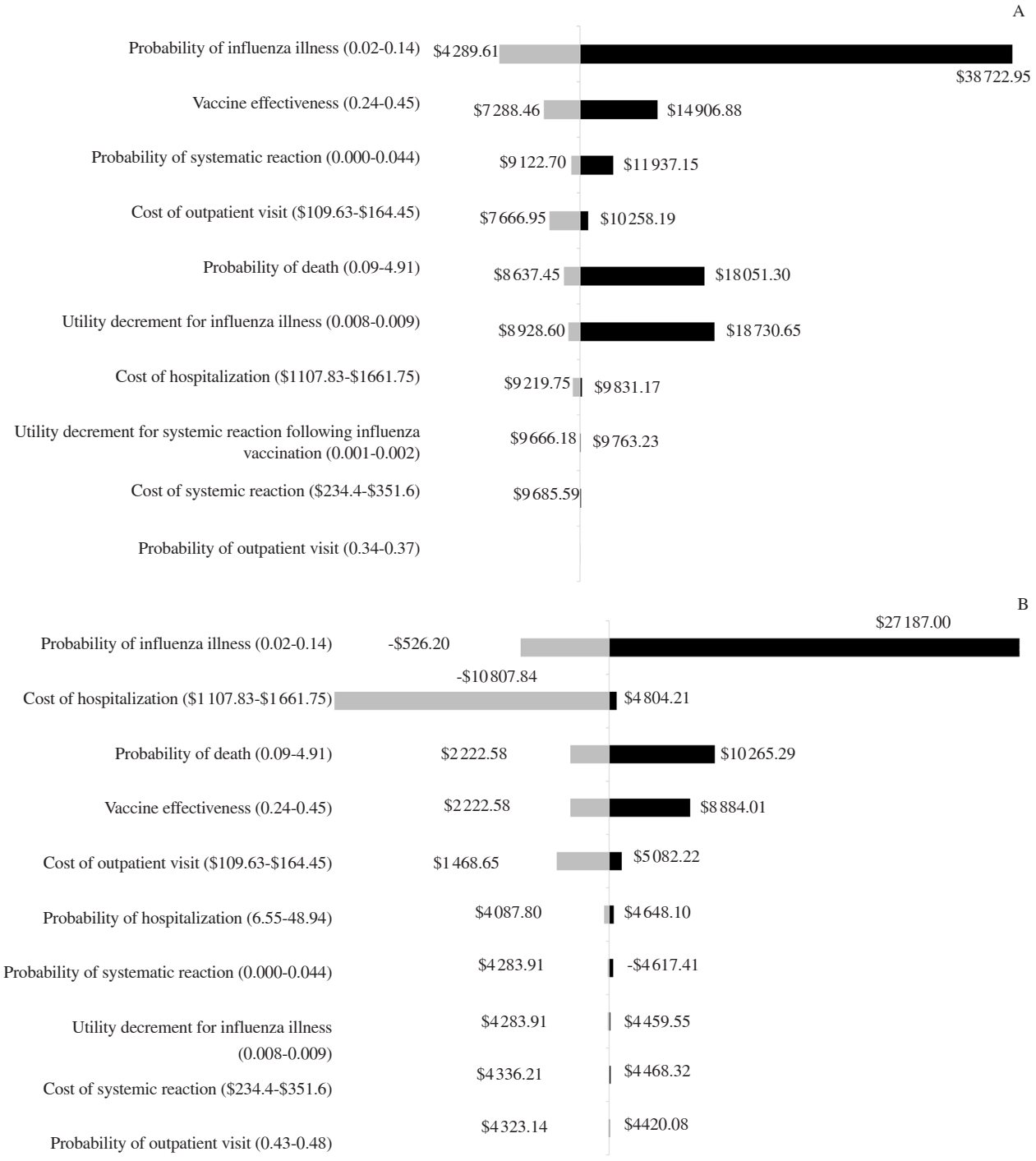

Figure 2. One-way sensitivity analysis for vaccination compared to no vaccination for adults aged 18-49 years with non-high risk status (A) and high risk status (B). $: US dollars.

probabilistic sensitivity analyses (Figure 3). Cost-effectiveness acceptability curves characterize uncertainty in economic evaluations and represent the probability that an intervention is cost-effective under a range of cost-effectiveness thresholds. Under the threshold of $5 000/QALY, the probability that annual influenza vaccination strategy would range from 7.51% (children aged from 6 months to 4 years) to 81.12% (adults aged 50-64 years) for non-high risk subgroups, and ranged from 34.32% (children aged from 6 months to 4 years) to 99.87% (older person aged ≥65 years) for high risk subgroups.

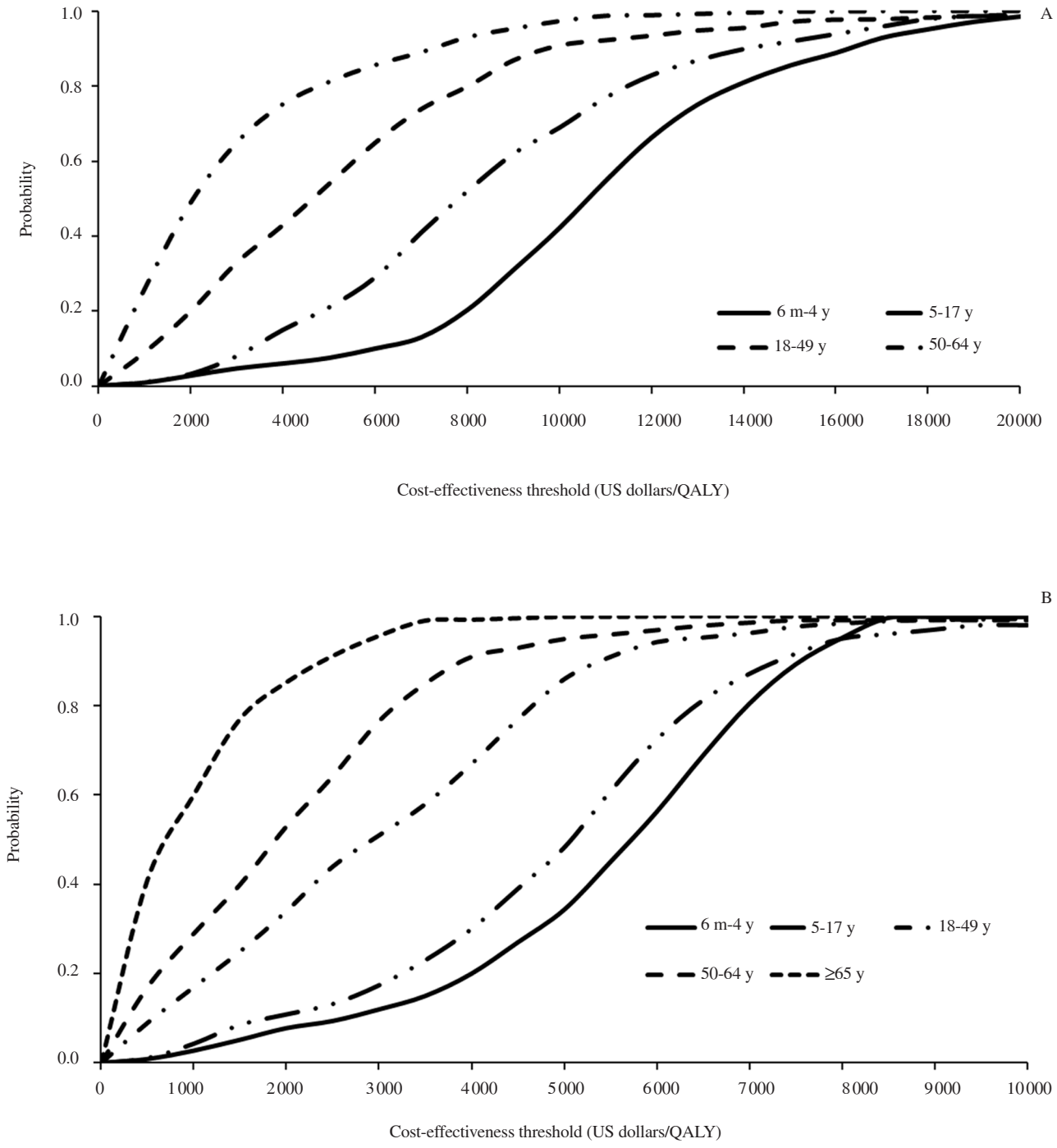

Figure 3. Probabilistic sensitivity analyses for non-high risk groups (A) high risk groups (B); m: months, y: years.

4. Discussion

Seasonal influenza imposes a significant health and economic burden in China, particularly in elders with high risk for severe consequences of infection. We evaluated the cost-effectiveness of annual IIV3 universal vaccination strategy among population aged ≥6 months, under the Zhejiang province-specific demographic data. The highest benefit of annual IIV vaccination program was observed in elders aged ≥65 years with high risk, and this strategy could also induce the net health gains for all other subgroups, with net cost incurred simultaneously. In terms of health gains from IIV3, our findings were consistent with results from previous reports[32-37], which demonstrated IIV3 could reduce the number of influenza cases, hospitalizations, and deaths, and being cost saving. Our analysis indicated that the ICER was cost-saving among elders aged ≥65 years with high risk. We assumed the reason isthe high incidence of death or complication due to influenza infection among this vulnerable subgroup and more death or severe cases would be averted from IIV3 vaccination.

Influenza vaccination strategy required a net investment to produce health benefits for most subgroups in this study. Previous reports had indicated that, comparing with no intervention, IIV3 was cost-effective when it was used in healthy children, healthy adults aged 50-64 years and the elderly[38-40]. In our study, the ICER ranged from $6 268/QALY to $11 260/QALY for age groups with non-high risk, and ranged from cost-saving to $5 260/QALY for age groups with high risk. In 2023, the Gross Domestic Product (GDP) per capita of Zhejiang province was $17 745, which was higher than the ICERs for all age group with or not with high risk. It demonstrated the annual IIV3 vaccination strategy was still cost-effective if we used one time of the GDP per capita.

The vaccine effectiveness for elders aged ≥65 years used in our model was lower than previously assumed[41], which might influence the economic value of influenza vaccination strategy. In the base-case analysis, we found influenza vaccination for elders aged ≥65 years was cost-saving, assuming the vaccine effectiveness was at 27%. Given the substantial burden of influenza illness in elders, our results demonstrated that influenza vaccination is necessary for the older age group even if vaccine effectiveness was lower than previously assumed.

Studies on the cost-effectiveness of influenza vaccination program among healthy working-age (18-49 years) adults in the China were rare. Among the small number of health economic studies from other countries, influenza vaccination was generally favorable for this age group[42,43]. However, these reports assumed that the vaccination scenario was in low-cost settings and the outcomes varied. These reports also found that parameters including incidence of influenza, cost of vaccination, vaccination effectiveness, productivity loss and daily productivity would significantly influence the cost-effectiveness results, which were similar with the findings in our analysis.

The cost-effectiveness thresholds of $5 000/ QALY for this subgroup were applied in our sensitive analysis, which were lower than the commonly used effectiveness thresholds used in previous studies. For example, the threshold range of GB€ 20 000 to 30 000 was considered as cost-effective in a report from Great Britain[44]. Canadian Agency for Drugs and Technologies in Health used a threshold of CAD$ 50 000-100 000 in the pharmaceutical health economics evaluation[45]. Also, a threshold of US$ 50 000 was commonly used in similar studies in US[46]. There were several reasons for the different choices of the threshold settings. First, it might be due to the lower probability of influenza case and influenza-related complication, underscoring the potential economic value of influenza vaccination in different countries, especially for high-risk individuals. For example, a cost-effectiveness study of influenza vaccination among pregnant women found the influenza vaccination resulted in an ICER of $ 260 000/QALY during a very low incidence season[47]. Second, it would be related to the difference in social and economic development between Zhejiang province and these developed countries.

The second panel on cost-effectiveness in health and medicine recommended that productivity cost should be included in the numerator of the formula of calculating ICER as a monetary term[48]. However, other reports would not include the productivity loss into cost since it would be captured in the QALY loss with influenza health states, and it might cause a repeat counting and inflate the cost[49,50]. However, we assumed that the loss in QALYs associated with influenza only considered the life and adjusted life losses due to the disease itself when these data came from field investigation, which might not include the indirect cost. Moreover, the annual influenza vaccination program would be more attractive from the social perspective if the productivity losses included in the analysis.

There were several limitations to this study. First, indirect effects of reduced transmission were not included in this study because assumptions about the effectiveness of vaccines to reduce transmission were still uncertain for seasonal influenza. If these indirect effects were included, the results would be more favorable for vaccination. Second, our model did not include family spillover effects of illness, such as the burden of informal caregiving. If these effects were included, the cost-effectiveness of vaccination would also be more favorable. Third, the difference in the probability of experiencing symptomatic influenza among individuals with or without high risk was not considered in this analysis, and if a high risk individual was at greater risk of experiencing symptomatic compared to a non-high risk individual, then vaccination would be more favorable for high risk subgroups. Lastly, the analysis did not include the differences in duration of symptoms and complications from influenza between vaccinated versus unvaccinated individual.

If vaccinated individual experienced a shorter duration of illness compared to unvaccinated individual, then vaccination would be more economically attractive.

In conclusion, this study provided the crucial information for policy-makers assessing the universal influenza vaccination recommendation. Our findings indicated that influenza vaccination produces cost-effectiveness ratios that were less than commonly used cost-effectiveness thresholds for all subgroups. After incorporating updated epidemiologic and vaccine effectiveness data, annual influenza vaccination remained cost-effective for all-age and different risk status groups from a societal perspective.

Conflict of interest statement

The authors declare that they have no competing interests.

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Authors' contributions

YH and ZY developed the specific study protocol, constructed the model for cost effectiveness analysis. CJ collaborated in the study protocol and in the construction and refinement of the model. JZ and YX contributed to the collection of data required for the input parameters. YH and ZY initiated the study design, supervised the project, and directed the analysis and manuscript writing. All authors had carefully revised the draft of the manuscript.

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