THE UNIVERSITY *of* EDINBURGH

Cost-effectiveness of introducing national seasonal influenza vaccination for adults aged 60 years and above in mainland China: a modelling analysis

Citation for published version:
Yang, J, Atkins, KE, Feng, L, Baguelin, M, Wu, P, Yan, H, Lau, EHY, Wu, JT, Liu, Y, Cowling, BJ, Jit, M & Yu, H 2020, 'Cost-effectiveness of introducing national seasonal influenza vaccination for adults aged 60 years and above in mainland China: a modelling analysis', *BMC Medicine*, vol. 18, no. 1. https://doi.org/10.1186/s12916-020-01545-6

Digital Object Identifier (DOI):
10.1186/s12916-020-01545-6

Published In:
BMC Medicine

Cost-effectiveness of introducing national seasonal influenza vaccination for adults aged 60 years and above in mainland China

Juan Yang[1], Katherine E. Atkins [2,3,4], Luzhao Feng[5], Marc Baguelin[2,3,6], Peng Wu[7], Han Yan[1], Eric H. Y. Lau[7], Joseph T. Wu[7], Yang Liu[2,3], Benjamin J. Cowling[7], Mark Jit[2,3,7,8]*, Hongjie Yu[1]*

Affiliations:

1. School of Public Health, Fudan University, Key Laboratory of Public Health Safety, Ministry of Education, Shanghai, China

2. Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

3. Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, United Kingdom

4. Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, United Kingdom

5. Key Laboratory of Surveillance and Early-warning on Infectious Disease, Division of Infectious Disease, Chinese Center for Disease Control and Prevention, Beijing, China

6. MRC Centre for Global Infectious Disease Analysis, School of Public Health, Imperial College London, London, United Kingdom

7. WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

8. Modelling and Economics Unit, Public Health England, London, United Kingdom

*Joint senior authors with equal contribution

Hongjie Yu, School of Public Health, Fudan University, Key Laboratory of Public Health Safety, Ministry of Education, Shanghai, China, Tel: +86 21 54237628; E-mail: yhj@fudan.edu.cn

Word count (abstract): 250
Word count (main text): 3,777
Running head: Cost-effectiveness of influenza vaccination in China

Abstract

Background China has an ageing population with an increasing number of adults aged ≥60 years. Influenza causes a heavy disease burden in older adults, but can be alleviated by vaccination. We assessed the cost-effectiveness of a potential government-funded seasonal influenza vaccination program in older adults in China.

Methods We characterized the health and economic impact of a fully-funded influenza vaccination program for older adults using China specific influenza disease burden, and related cost data, etc. Using a decision tree model, we calculated the incremental costs per quality-adjusted life year (QALY) gained of vaccination from the societal perspective, at a willingness-to-pay threshold equivalent to GDP per capita (US$8,840).

Findings Compared to current self-paid vaccination, a fully-funded vaccination program is expected to prevent 19,812 (95% uncertainty interval, 7,150-35,783) influenza-like-illness outpatient consultations, 9,418 (3,386-17,068) severe acute respiratory infection hospitalizations and 8,800 (5,300-11,667) respiratory excess deaths due to influenza, and gain 70,212 (42,106-93,635) QALYs. Nationally, the incremental costs per QALY gained of the vaccination program is US$4,832 (3,460-8,307), with a 98% probability of being cost-effective. However, variations exist between geographical regions, with Northeast and Central China having lower probabilities of cost-effectiveness.

Interpretation Our results support the implementation of a government fully-funded older adult vaccination program in China. The regional analysis provides results across settings that may be relevant to other countries with similar disease burden and economic status, especially for low- and middle-income countries where such analysis is limited.

Funding National Science Fund for Distinguished Young Scholars, and UK National Institute of Health Research.

1. Introduction

Seasonal influenza is a major cause of mortality, with recent estimates suggesting that 291 000–646 000 influenza-associated respiratory deaths occur globally each year[1]. Older adults are at increased risk of hospitalization or death if infected, and thus are included in the recommended groups for annual influenza vaccination by the World Health Organization (WHO)[2]. The World Health Assembly set a target of attaining vaccination coverage of 75% in this group by 2010 [3]. Most high income countries and many upper-middle income countries, like Thailand and Brazil, have incorporated seasonal influenza vaccination for older adults into their National Immunization Program, which has significantly increased vaccination uptake[4-6].

As the world's most populous country, China has more adults ≥ 60 years (>210 million in 2016) than any other country, accounting for nearly a quarter of the global total. China is also ageing rapidly; adults ≥60 years account for 15% of the population in 2016[7] and will increased to 26% by 2030[8]. Influenza caused 66-105 severe acute respiratory infections (SARI) hospitalizations per 100,000 adults ≥60 years in China[9,10]. Annually, over 80% of influenza-related excess deaths occurred in older adults[11,12], with an average excess respiratory mortality rate per season estimated at 38·5 (95% confidence interval, 95%CI 36·8-40·2) per 100,000 person between 2010-15[12]. However, there is no nationwide government-funded influenza vaccination program for older adults in China, and the cost of vaccination is completely borne by individuals. This self-paid vaccination system contributes to an extremely low vaccine uptake of 4% in this age group, far behind the target of 75%[13]. Only a handful of relatively wealthy cities provide free influenza vaccination for older adults paid by local governments[14]. For example, since 2007, Beijing has provided free influenza vaccination to older adults, leading to the uptake reaching 39% in 2012[15].

Following a health scare involving improper refrigeration of transported vaccines sold privately nationwide in 2016[16], the State Council of China recommended acceleration of the inclusion into the National Immunization Program of vaccines currently sold in the private sector[17]. The new vaccine administration law in 2019 requires establishing a 'national dynamic adjustment mechanism' for inclusion/exclusion of vaccines into National Immunization Program[18]. Both the State Council and National Immunization Advisory Committee also recommended taking into consideration the cost-effectiveness of vaccination alongside traditional considerations of vaccine efficacy and safety for vaccine policy-making[19].

A systematic review of cost-effectiveness studies of influenza vaccination showed that globally a third of studies (8/27) found vaccination in older adults to be cost-saving, and most of the remainder found vaccination to be cost-effective[20]. However, to date no comprehensive study has been conducted in mainland China, where the economic impact of fully-funded vaccination programs may differ greatly across regions due to large variations in influenza seasonality, disease burden, demographic structure, and social economic development[11,21,22]. Hence, the objective of this study is to answer the question of whether a fully-funded influenza vaccination program for nearly a quarter of the world's older adult population is an efficient use of resources in mainland China, and to further explore whether variations in this result exist across geographical regions.

2. Methods

Following WHO guidance on the economic evaluation of influenza vaccination[23], we performed a cost-effectiveness analysis of a government-funded influenza vaccination program for adults ≥60 years compared to the status quo of vaccinees paying out-of-pocket (hereafter "fully-funded vaccination program" and "self-paid vaccination program" respectively) from the societal perspectives. As most costs and effects due to influenza occur during a single influenza season, we used a time horizon of one year, with the exception of tracking all the years of life lost when a patient died of influenza-related causes.

2.1 Decision tree model

We developed a static decision tree model (Figure 1) to calculate the per person costs of vaccination, per person costs due to influenza, and per person health utility loss due to influenza. From these estimates, we estimated the impact of the fully-funded program compared to self-paid vaccination on health and economic outcomes at the regional and national level. We then used these outcomes to calculate the incremental cost-effectiveness of the fully-funded program. Detailed methods are shown in Supplementary Materials 1.

As current vaccine coverage is only 4% and is concentrated in a few highly-developed cities with local government funding[13], we assumed the probability of being vaccinated was zero under the status quo. There is significant uncertainty in the vaccine uptake that may be achieved in a potential fully-funded vaccination program. The experience of Beijing showed that the uptake in older adults increased substantially from 2% in 1999 to 39% in 2012[15,24] after fully-funded influenza vaccination was offered in 2007. It is likely that the uptake in other less densely-populated and developed provinces would not increase as quickly as Beijing, the capital of China where residents likely to have greater access to health care facilities. We therefore used a conservative coverage assumption of 30% in the analysis.

An older adult is assumed to have a risk of acquiring a symptomatic influenza infection annually. Someone with symptomatic influenza then has a probability of seeking medical treatment, including self-medication, seeking healthcare in a community or township health service center, consulting a doctor in an outpatient department, or being hospitalized. Each infected person also has a probability of dying of influenza-related causes, whether or not the person has received healthcare.

The models were stratified by area (rural/urban) and geographical regions (Figure S1: Northern, Northeast, Northwest, Eastern, Central, Southwest, and Southern). All analyses were performed in R version 3·5·0 (https://www.r-project.org).

2.2 Data sources

2.2.1 Population

The model tracked older adults aged 60-64, 65-69, 70-74, 75-79, and ≥80 years. The age-specific population size in 2016 was obtained from the National Bureau of Statistics in China, and stratified by area (rural/urban) using the proportion of older persons living in urban areas reported in the 2010 Population Census of China[25]. (Supplementary Materials 3)

Older adults were further split into high- and low-risk groups. High-risk individuals are defined as those with an increased risk of hospitalization or death if infected by influenza due to underlying medical conditions as listed in the WHO influenza vaccine guidelines, including chronic obstructive pulmonary disease, asthma, diabetes, and chronic cardiac disease, etc.[26] The remaining population was categorized as low-risk. The probability of an older adult having at least one underlying medical disease was estimated from the results of the China Health and Retirement Longitudinal Study[27,28], a nationally representative study on health status in older people. (Supplementary Materials 4).

2.2.2 Influenza-related disease burden

Influenza-like-illness (ILI) consultations due to influenza

The yearly average risk of ILI-related primary care or outpatient consultations due to influenza in China was estimated to be 0·9 per 1,000 (95% CI 0·4-1·5) between 2010-2015[29]. The influenza-related ILI consultation risk varied significantly cross provinces (Table S2), ranging from 10 to 690 per 100,000.

Hospitalization

It was found that influenza was associated with an estimated 89 (95%CI 85-90) SARI hospitalizations per 100,000 for individuals ≥65 years during 2011-2012 in Jingzhou (a city in Southern China)[9]. The rates were 105 (95%CI 85-129) and 66 (95%CI 50-86) per 100,000 people in Beijing (a province in Northern China) during the 2014-2015 and 2015-2016 seasons, respectively[10]. In our study, the influenza-related hospitalization rates in other Southern and Northern provinces (Figure S1) were estimated using the local influenza-related ILI consultation rate multiplied by the ratio of influenza-related SARI hospitalization rate to influenza-related ILI consultation rate separately in Jingzhou and Beijing[9,10,29].

Mortality

The national average influenza-associated excess mortality attributable to respiratory diseases was estimated to be 38·5 (95%CI 36·8-40·2) per 100,000 between 2010-2015 in China[12]. Variation (19.0-83.2/100,000) was observed across provinces (Table S2).

We found a clear positive relationship between Gross Regional Product per capita and influenza-related ILI consultation risk (Pearson correlation coefficient=0.83, $p<0.05$). This variation is likely to be explained by differences in health care access or under-reporting. In the base case analysis, we used original influenza-related ILI consultation and excess mortality rates as reported for each province in the literatures [12,29]. This assumes that the differences between provinces are genuine and are explained by differences in influenza epidemiology.

The highest influenza-related ILI consultation risk occurs in Shanghai (690/100,000), a high-income province with very good health care access and surveillance system and. Accordingly, in the scenario analyses, we assumed every province has the same risk as Shanghai based on the "under-reporting" hypothesis or assumed the differences are explained by differences in health care access (i.e., "health care access" hypothesis).

For excess mortality, we assumed every province has the same risk as the province with the highest risk, which is 83.2/100,000 in Gansu province[12]. A total of four scenario analyses were performed in this study, with detailed descriptions shown in Table 1.

A systematic review demonstrated that the presence of "any risk factor" (using the WHO risk factors definition[26]) was associated with an increased risk of hospital admission (odds ratio 3·39, 95%CI 2·60-4·42) and death (odds ratio 2·04, 95%CI 1·74-2·39) in influenza-related patients[30].

2.2.3 Healthcare seeking behavior

A household survey on health seeking behavior of adult patients with acute respiratory infections carried out in China during 11/2009-03/2010, found that: 1) in urban areas, 9·7% of acute respiratory infection cases did not seek any medical help, 66·0% self-medicated, or visited a doctor in community or township health centers, and the remaining 24·3% visited a doctor in county or higher level hospitals; 2) in rural areas, the relevant proportions were respectively 8·6%, 79·0% and 12·4%[31]. We assumed that influenza patients have the same healthcare seeking behaviors as acute respiratory infections cases.

2.2.4 Influenza-related costs

We used the average drug cost per outpatient in township healthcare centers (US$ 5·4 in 2017) and that in community healthcare centers (US$11·9 in 2017) as a proxy of the cost for self-medication of influenza patients in urban and rural areas, respectively[32]. We previously found the treatment costs for influenza-related outpatients and inpatients aged 60 years old and over were respectively US$129 (95% uncertainty interval, 95%UI 75-156) and US$2,735 (1,401-4,482) in East China in 2013[33]. The costs were extrapolated to other regions in China in proportion to the regional GDP per capita.

We also considered the lost productivity due to premature mortality attributable to influenza, which was estimated using the friction cost method. The length of the friction period was assumed to be three months, the elasticity of labor time versus production assumed to be 0·8, and the costs of filling a vacancy and training new personnel estimated to be US$357 in 2009[34,35]. The yearly income per capita of older adults (urban US$3,896; rural US$1,241) was obtained from the fourth survey of the living conditions of older adults in urban/rural China in 2014[36]. The labor force participation rates of older adults were derived from the 2010 Population Census of China[25]. All costs were adjusted and converted to US dollars in 2017 using the consumer price index and the exchange rate of 1 US$= 6·75 CNY[37].

2.2.5 Quality-adjusted life years (QALYs) lost

The number of QALYs lost due to influenza was calculated as the sum of QALYs lost due to non-fatal episodes plus life years lost due to fatal episodes. The duration of non-fatal episodes was assumed to be respectively 6·2 days (standard deviation, 2·2) and 16·0 days (10·7) for influenza-related outpatients and inpatients. Their associated health utility was separately estimated to be 0·5733 (95%UI 0·4650-0·6608) and 0.4128 (0·1793-0·6380)[38]. The background health utility (urban 0·7719-0·8071; rural 0·6943-0·7434) was obtained from the China Health and Retirement Longitudinal Study[39].

Life years lost due to fatal episodes were estimated based on risk-, area- and age-specific life expectancy. Life expectancy was calculated using the life table approach and mortality data in 2017 from China Health and Family Planning

Statistical Yearbook[32,40]. Life years lost were discounted at an annual rate of 3%[41]. (Supplementary Materials 6)

2.2.6 Vaccine effectiveness and cost

A recent meta-analysis of test-negative design case-control studies indicated that influenza vaccine is effective against laboratory confirmed influenza (odds ratio 0·48; 95% CI 0·39-0·59) in older adults when the vaccine strains closely match the circulating influenza viruses, and also had significant effectiveness when vaccine is poorly matched (odds ratio 0·64; 95% CI 0·52-0·78)[42]. We conservatively used the efficacy of poorly-matched vaccines in the baseline analysis. Adverse effects associated with influenza vaccination were not considered as serious adverse events are extremely rare[43].

The procurement cost of influenza vaccination (not including vaccine logistic and administration costs) in 2013 was US$5·73 per dose (95%UI 5·43-6·03) for the 0·50ml formulation Trivalent Inactivated influenza Vaccine[14].

2.3 Outcomes measures

In this study, we calculated the incremental costs per QALY gained of vaccination, and evaluated the health and economic impact of fully-funded influenza vaccination at the national and seven regional levels, respectively. Because China does not have an official threshold for cost-effectiveness, we used a willingness-to-pay threshold of the GDP per capita (US$8,840 in 2017) in the base case analysis, and a more stringent threshold of US$3,780-US$5,880 per QALY gained proposed by University of York economists[44] to construct cost-effectiveness acceptability curves. Due to the unavailability of vaccine logistic and administration costs, only vaccine procurement costs were included in the base case and sensitivity analyses. We further performed analyses for threshold vaccination costs (TVC), below which fully-funded vaccination program would be considered cost-effective.

2.4 Sensitivity analysis

We performed probabilistic sensitivity analyses to explore the influence of all parameters on ICERs. This was done using Monte Carlo sampling with applicable distributions for different parameters (Table 2), drawing 10,000 samples, then calculating the median, and 95% UIs for the ICERs based on the 2·5th and 97·5th percentiles of the 10,000 simulations. Scenario sensitivity analyses were also conducted:1) from the health system perspective (only considering the direct medical costs for influenza patients), 2) using well-matched vaccine effectiveness [42], and 3) using a discount rate of zero for QALYs loss as recommended by WHO guidelines[45].

3. Results

3.1 Impact and cost effectiveness in the base case scenario

At the national level, a total of 63·4 million older adults in China are expected to be vaccinated annually. Vaccination is expected to prevent 19,812 (95%UI 7,150-35,783) influenza-related ILI outpatient consultations, 9,418 (3,386-17,068) influenza-related SARI hospitalizations and 8,800 (5,300-11,667) influenza-related deaths due to respiratory diseases, with 40%, 69% and 57% occurring in high-risk groups (Figure 2 an S4).

The fully-funded vaccination program is estimated to cost US$ 363 (344-382) million, but gain 70,212 (42,106-93,635) QALYs, 98% of which were due to influenza-related excess deaths averted (Figure 2). 38% of the increment cost, and 54% of incremental QALYs occurs in high-risk groups (Figure S4). Using the GDP per capita as a threshold, the fully-funded vaccination in older adults in China is cost-effective with an ICER of US$4,832 (3,460-8,307) per QALY gained. The TVC is US$10·19 (6·08-13·65), under which the fully-funded vaccination program is cost effective using GDP per capita as the willingness-to-pay threshold (Figure 3).

Substantial variations in health and economic outcomes are observed across regions (Figure 2). Except in Northeast China (US$8,945), the median ICER (US$2,691-7,115) is below the GDP per capita and hence cost-effective. The TVC in Northeast and Central China is lower than the national average, decreasing to US$5·66 (3·41-7·70) and US$7·06 (4·15-9·66) (Figure 3).

3.2 Probabilistic sensitivity analyses

At the national level, 98% of Monte Carlo samples are considered cost-effective under base case assumptions with a threshold of GDP per capita. However, significant differences are observed for regions. For Northeast and Central China, the proportion respectively reduces to 48% and 82%. While for other regions, the probability is over 96% (Figure 4). Using a much more stringent threshold of US$3,780-5,880 per QALY gained[44], the probability of cost-effective for vaccination decreases to 9%-80% at the national level. Similar patterns are observed across regions (Figure S6).

3.3 Scenario analyses

Compared to the base case scenario, the influenza-related excess mortality due to respiratory diseases increased 1-3 fold in Central, Northeast and Southwest China, while only 47%-86% for other regions in scenario 1 and 2 . The low probability of being cost-effective (around 48%) is only observed for Northeast China in base case and scenario 2 (Figure 4). Compared to the base case scenario, TVC increases by 55%-330% in scenario 1 and 2, and 4%-24% in scenario 4, while decreases slightly in scenario 3 (Figure 3).

Compared to the societal perspective analysis above, ICERs increase slightly (mostly by <10% depending on region and scenario) from a healthcare provider perspective (Figure S7-9). Vaccine effectiveness and discount rate have a high impact on ICERs. When the vaccine is well matched circulating influenza strains, the fully-funded vaccination program is 100% cost effective across all regions (Figure S10-12). When the discount rate for QALYs loss is zero, the fully-funded vaccination program is cost effective across all regions, at a probability of >90% except for Northern China in base case and scenario 3 (around 80%)(Figure S13-15).

Compared to the base case analysis (with a mismatched vaccine and a discount rate of 3%) from the societal perspective, the TVC decreases by less than 5% from the healthcare provider perspective, while it increases by 44%-45% when vaccine strains match the circulating strains, and increases by 18%-21% when discount rate is zero for QALYs loss (Figure 3).

4. Discussion

The provision and management of vaccines in China is currently undergoing regulatory reforms[16,46]. Expanding China's government-funded vaccination programs is now recommended by both WHO and the State Council of China[17,47]. In 2019, the influenza vaccine was one of the vaccines that went through comprehensive evaluation by the National Immunisation Advisory Committee of China for inclusion into the National Immunisation Program as a fully government-funded vaccine. A first step towards this could be considering vaccination for older adults due to their higher risk of influenza-related hospitalization and mortality. Our analysis comprehensively evaluates the health and economic impact of a potential fully-funded influenza vaccination program in older adults. It shows that vaccinating older adults in China is cost-effective, with an ICER of US$ 4,832 per QALY gained (lower than GDP per capita), despite conservative assumptions about vaccine effectiveness assumed in the base case scenario. However, we find that variations in health and economic impact exist across regions.

In our study, the fully-funded vaccination program could reduce both QALY loss and productivity loss due to premature deaths. While productivity loss only contributes to <2% of the decrease in total costs , the relevant QALY loss averted contributes to >96% in total QALYs saved. Accordingly, variation in influenza-related respiratory excess mortality across regions is a significant factor for different ICERs observed here (base case vs. scenario 1, and 2). Our analysis demonstrates that in the base case analysis, the probability of being cost-effective for the fully-funded influenza vaccination program is much lower in regions with lower reported mortality burden than that with heavy influenza excess mortality burden (e.g., lower in Northeast compared to. Northern China) [12]. The influenza mortality in Northeast China may genuinely be lower due to lower population density and reduced air pollution. On the other hand, it may simply appear lower due to factors such as patients seeking advanced healthcare in neighbouring developed regions[12] and poor quality of influenza and death surveillance. Since the two sets of potential reasons for lower mortality are difficult to disentangle, we should be very cautious in interpreting regional-level economic results. This highlights the importance of improved influenza surveillance, particularly in less developed regions of China, in order to better target influenza control programs. Variations in influenza-related ILI consultation only have slightly impact on the ICERs (base case vs. scenario 4).

In Northeast China, the fully-funded influenza vaccination program is considered cost-effective if TVC is respectively below US$5·7 in the base case analysis. We used the private sector vaccine cost in the model, which is US$5·73 per dose currently[14], much higher than most of the vaccines currently used in the National Immunisation Program[48]. Several Chinese manufactures produce influenza vaccines in Northeast China[43]. A government-funded influenza vaccination program using local manufactures' vaccines is likely to have lower delivery costs due to economies of scale and lower procurement costs due to increased consumer bargaining power. That will certainly increase the likelihood that the fully-funded influenza vaccination is cost-effective in this region.

Only one study to date has assessed the cost-effectiveness of influenza vaccination among older adults in China[49]. This study had a number of limitations: (i)it used influenza-related outpatient and hospitalization rates in the US, which may not be good proxies for relevant rates in China due to the different influenza seasonality, virus activity, and health seeking behavior, etc.[21] And (ii) it used influenza-related mortality before 2009 influenza pandemic in China, even though the burden has changed due to the displacement of seasonal A(H1N1) virus after pandemic[11,12]. With these shortcomings, the paper suggested that government-funded influenza vaccination was <50% likely to be cost-effective, when compared to a threshold of one times GDP per capita. In our study, we used the most recent China-specific post-2009 pandemic data, including influenza-related outpatient, hospitalization and mortality rates.

The number of excess respiratory deaths[29] used in this study may not fully capture all influenza–associated deaths because influenza virus infections not only cause respiratory deaths, but also deaths from other diseases such as cardiovascular diseases, diabetes, and renal diseases[11]. Accordingly, vaccination could be even more cost-effective than presented here.

A limitation of our study is that the influenza-related SARI hospitalization rate is only available in one city each in Southern and Northern China[9,10]. These two cities may not fully represent the hospitalization rate across China. We used the ratio of the influenza-related SARI hospitalization rate to influenza-related ILI consultation rate separately in Jingzhou, Hubei and Beijing as a multiplier to estimate the influenza-related SARI hospitalization rate for the rest of Southern and Northern China, respectively. However, it may not be a good proxy due to different health seeking behaviors especially between areas with varying levels of socioeconomic development, and health service provision.

China's first vaccine administration law allows provincial governments to add additional vaccines into their local fully-funded vaccines list on the basis of local disease burden[18]. Until now, only a few highly-developed provincial- and prefecture-level cities have offered fully-funded influenza vaccination for older adults (e.g., Beijing and Shenzhen).These local initiatives have achieved remarkable increases in local vaccine uptake[14,15]. However, expanding such fully-funded vaccination to the entire population or even large regions of China would require large budget allocations. Because of that, there is a need for detailed cost-effectiveness analysis to determine if such a move is good value for money. Hence our results fill a key evidence gap needed by decision-makers in China. Due to large apparent variations in influenza disease burden, and socioeconomic development level across regions, our regional analyses could also provide information on the cost-effectiveness of fully-funded influenza vaccination that may be relevant to other countries with similar disease burden and economic status, especially low- and middle-income countries where cost-effectiveness analysis is limited[20].

Research in context

Evidence before this study

Seasonal influenza vaccination in older adults has been found to be cost-effective in many middle- and high-income countries, and has been introduced into the vaccine schedules of many such countries. In contrast, in most of China influenza vaccines are only available in the private sector and have very low uptake, even though China has more adults aged 60 years and over than any other country and is ageing rapidly. A previous systematic review (Pan X, *et al.* Systematic review of economic evaluations of vaccination programs in mainland China: Are they sufficient to inform decision making? Vaccine, 2015.) shows no cost-effective analysis of influenza vaccination in older adults has been conducted in mainland China till August, 2015. We further searched PubMed, China National Knowledge Infrastructure and Wanfang between August 4, 2015 and November 20, 2019, using MeSH terms and key words, including “influenza”, “vaccine”, “economic evaluation” or “cost”, and “China”. Only one study in Chinese (Chen C, *et al*. Cost‐effective analysis of seasonal influenza vaccine in elderly Chinese population. Chin J Prev Med, 2019) has been published. This used influenza outpatient and hospitalization burden in the US as a proxy for the burden in China to evaluate the government-funded influenza vaccination programme among the older adults at the national level. The study found that government-funded influenza vaccination has a low probability of being cost-effective (<50%) when using one times GDP per capita as the cost-effectiveness threshold.

Added value of this study

We assessed the epidemiological impact and cost-effectiveness of a potential government fully-funded influenza vaccination program using China-specific disease burden of influenza at both the national and regional level. Our findings show that vaccination program is cost-effective at the national level in China. However, variations exist among geographic regions, with Northeast China having a lower probability of being cost-effective. However, this may be at least partly due to differences in surveillance quality across regions. In Northern China, the fully-funded influenza vaccination program is cost-effective if vaccination cost is below US$5·66.

Implications of all the available evidence

Our findings support implementing a fully government funded influenza vaccination program in mainland China. It also highlights the variation in health and economic effects of vaccination across China due to variations in influenza seasonality, disease burden, demographic structure, and socioeconomic development. These results are likely to be vital for policy making since the State Council of China has recommended acceleration of the inclusion into the national immunization program of vaccines currently sold in the private sector.

Declaration of interests

YH has received investigator-initiated research funding from Sanof Pasteur, GlaxoSmithKline, bioMérieux Diagnostic Product (Shanghai), and Yichang HEC Changjiang Pharmaceutical Company. BJC received honoraria from Sanofi Pasteur and Roche for consulting on influenza treatment and prevention.

Contributors

HY and MJ designed the study. JY, LF, PW, HY, EHYL, JTW, YL, and BJC collected data. JY, KEA, and MB developed the model. JY analyzed the data. JY, HY and MJ wrote the drafts of the manuscript, and interpreted the findings. All authors commented on and revised drafts of the manuscript. All authors read and approved the final report.

Acknowledgement

This study was funded by the National Science Fund for Distinguished Young Scholars (grant no. 81525023), the National Natural Science Foundation of China (grant no. 81903373), the National Science and Technology Major Project of China (grant no. 2017ZX10103009-005), and the National Institute for Health Research (NIHR) (grant no. 16/137/109) using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the UK Department of Health and Social Care.

Table 1. Description of base case and scenario analyses.

Analyses	Influenza-related ILI consultation [29]	Influenza-associated excess mortality attributable to respiratory diseases [12]
Base case	Used original rate as reported for each province in the literature	Used original rate as reported for each province in the literature
Scenario 1	Used original rate as reported for each province in the literature, and assumed the difference between any other province and Shanghai is due to difference in health care access (i.e., "health care access" hypothesis)	Assumed every province has the same risk as Gansu Province, with the highest rate of 83.2/100,000
Scenario 2	Assumed every province has the same risk as Shanghai, with the highest rate of 690/100,000	Assumed every province has the same risk as Gansu Province, with the highest rate of 83.2/100,000
Scenario 3	Used original rate as reported for each province in the literature, and assumed the difference between any other province and Shanghai is due to difference in health care access (i.e., "health care access" hypothesis)	Used original rate as reported for each province in the literature
Scenario 4	Assumed every province has the same risk as Shanghai, with the highest rate of 690/100,000	Used original rate as reported for each province in the literature

Table 2. Key model parameter distributions.

Parameter	Mean (Range/SD)*	Distribution
Proportion of high-risk groups	Supplementary Materials 4, Fig S3	Beta
Flu-related ILI consultation rate[29]	Supplementary Materials 5, Table S2	Normal
Flu-related SARI hospitalization (per 100,000)[9]		
Beijing (2013-2014)	105 (95%CI 85-129)	Normal with μ=105, sd=11·22
Beijing (2014-2015)	66 (95%CI 50-86)	Normal with μ=66, sd=9·18
Jingzhou, Hubei province (2011-2012)	89 (95%CI 85-90)	Uniform (min=85/100,000, max=90/100,000)
Flu-related respiratory excess mortality[12]	Supplementary Materials 5, Table S2	Lognormal
Healthcare seeking behaviour (%)[31]		
Probability of no-healthcare-use	Urban: 9·7, Rural: 8·6	Urban: Dirichlet with α1=107, α2=704, α3=269, Rural: Dirichlet with α1=43, α2=394, α3=62
Probability of self-treatment, seeking care in Community /Township Health Service Centers	Urban: 66·0, Rural: 79·0	
Probability of visiting doctors in county-level and above hospitals	Urban: 24·3, Rural: 12·4	
Odds ratio of influenza-related hospitalization in high-risk groups compared to low-risk groups[30]	3·39	Lognormal with μ=1·22, sd=0·14
Odds ratio of influenza-related death in high-risk groups compared to low-risk groups[30]	2·04	Lognormal with μ=0·71, sd=0·08
Vaccine cost (US$ in 2013)[14]	5·73 (95%UI 5·43-6·03)	Bootstrap from data on influenza vaccine cost
Influenza outpatients visits and hospitalization costs(US$ in 2013)[33]	Outpatients: 129 (95%UI 75-156) Inpatients: 2,735 (95%UI 1,401-4,482)	Bootstrap from data on national retrospective survey
Duration of influenza episode for outpatients and inpatients (days)[38]	Outpatients: 6·2 (SD 2·2) Inpatients: 16·0 (SD 10·7)	Bootstrap from data on national retrospective survey
Utility of influenza outpatients and inpatients[38]	Outpatients: 0·5733 (95%UI 0·4650-0·6608) Inpatients: 0·4128 (95%UI 0·1793-0·6380)	Bootstrap from data on national retrospective survey
Background health utility[39]	Urban 60-74 years: 0·8071 (SD 0·0039); ≥75 years: 0·7719 (SD 0·0093) Rural 60-74 years: 0·7434 (SD 0·0031); ≥75 years: 0·6943 (SD 0·0078)	Normal distribution
Risk of infected from influenza in vaccinated group vs. unvaccinated group (Odds ratio)[42]	0·64 (0·52-0·78)	Lognormal with μ=-0·45, sd=0·10

* used in one-way sensitivity analysis. SD denotes standard deviation; 95%CI denotes 95% confidence interval; 95%UI denotes 95% uncertainty interval calculated by bootstrap methods.

Figure captions

Figure 1. Decision tree model for influenza vaccination in older adults. Chance node 2 is the same as chance node 1, and chance node 4 is the same as chance node 3.

Figure 2. Epidemiological and economic impact of fully-funded influenza vaccination program in older adults, stratified by geographic regions, China

Figure 3. Threshold vaccination costs (TVC)

Figure 4. Monte Carlo simulation results on the cost-effectiveness for fully-funded vaccination program compared to self-paid vaccination program (grey line denotes China's GDP per capita in 2017 and circle denotes the 95%UI)

References

1. Iuliano AD, Roguski KM, Chang HH, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet* 2018; **391**(10127): 1285-300.

2. World Health Organiztion. Vaccines against influenza WHO position paper-November 2012. *Wkly Epidemiol Rec* 2012; **87**(47): 461-76.

3. Fifty-sixth World Health Assembly resolution WHA56.19. Prevention and control of influenza pandemics and annual epidemics. 28 May 2003. http://www.who.int/immunization/sage/1_WHA56_19_Prevention_and_control_of_influenza_pandemics.pdf. Accessed on September 25, 2015.

4. European Centre for Disease Prevention and Control. Seasonal influenza vaccination and antiviral use in EU/EEA Member States: Overview of vaccination recommendations for 2017-2018 and vaccination coverage rates for 2015-2016 and 2016-2017 influenza seasons. Available from: https://ecdc.europa.eu/sites/portal/files/documents/Seasonal-influenza-antiviral-use-EU-EEA-Member-States-December-2018_0.pdf. Accessed on February 8, 2019.

5. Bof de Andrade F, Sayuri Sato AP, Moura RF, Ferreira Antunes JL. Correlates of influenza vaccine uptake among community-dwelling older adults in Brazil. *Human vaccines & immunotherapeutics* 2017; **13**(1): 103-10.

6. Owusu JT, Prapasiri P, Ditsungnoen D, et al. Seasonal influenza vaccine coverage among high-risk populations in Thailand, 2010-2012. *Vaccine* 2015; **33**(5): 742-7.

7. United Nations. World population. https://population.un.org/wpp/Download/Standard/CSV/. Accesed on April3, 2019.

8. United Nations. World Population Ageing 2015. http://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf. Accessed on March 16, 2016.

9. Yu H, Huang J, Huai Y, et al. The substantial hospitalization burden of influenza in central China: surveillance for severe, acute respiratory infection, and influenza viruses, 2010-2012. *Influenza and other respiratory viruses* 2014 **8**(1): 53-65.

10. Zhang Y, Muscatello DJ, Wang Q, et al. Hospitalizations for Influenza-Associated Severe Acute Respiratory Infection, Beijing, China, 2014–2016. *Emerging Infectious Disease* 2018; **24**(11): 2098-102.

11. Yu H, Feng L, Viboud CG, et al. Regional variation in mortality impact of the 2009 A(H1N1) influenza pandemic in China. *Influenza and other respiratory viruses* 2013 **7**(6): 1350-60.

12. Li L, Liu Y, Wu P, et al. Influenza-associated excess respiratory mortality in China, 2010-15: a population-based study. *Lancet Public Health* 2019; **4**(9): e473-e81.

13. Zhou L, Su Q, Xu Z, et al. Seasonal influenza vaccination coverage rate of target groups in selected cities and provinces in China by season (2009/10 to 2011/12). *PLoS One* 2013; **8**(9): e73724.

14. Yang J, Atkins KE, Feng L, et al. Seasonal influenza vaccination in China: Landscape of diverse regional reimbursement policy, and budget impact analysis. *Vaccine* 2016; **34**(47): 5724-35.

15. Lv M, Fang R, Wu J, et al. The free vaccination policy of influenza in Beijing, China: The vaccine coverage and its associated factors. *Vaccine* 2016; **34**(18): 2135-40.

16. Parry J. Crackdown on illegal vaccine sales in China leads to 37 arrests. *BMJ* 2016; **352**: i1750.

17. Decision of the State Council on amending Regulations on Management of Vaccine Circulation and Inoculation (Order No. 668 of the State Council of the People's Republic of China).

http://www.gov.cn/zhengce/content/2016-04/25/content_5067597.htm>. Accessed on May 17, 2016.
18. The State Council of the People's Republic of China. http://www.gov.cn/xinwen/2019-06/30/content_5404540.htm. Accessed on June 30, 2019.
19. Steinhoff MC, Omer SB, Roy E, et al. Influenza immunization in pregnancy--antibody responses in mothers and infants. *N Engl J Med* 2010; **362**(17): 1644-6.
20. Peasah SK, Azziz-Baumgartner E, Breese J, Meltzer MI, MA. W. Influenza cost and cost-effectiveness studies globally--a review. *Vaccine* 2013; **31**(46): 5339-48.
21. Yu H, Alonso WJ, Feng L, et al. Characterization of regional influenza seasonality patterns in China and implications for vaccination strategies: spatio-temporal modeling of surveillance data. *Plos Med* 2013; **10**(11): e1001552.
22. Feng L, Shay DK, Jiang Y, et al. Influenza-associated mortality in temperate and subtropical Chinese cities, 2003-2008. *Bulletin of the World Health Organization* 2012; **90**(4): 279-88B.
23. World Health Organization. Guidance on the economic evaluation of influenza vaccination. http://www.who.int/immunization/research/development/influenza_maternal_immunization/en/index2.html. Accessed on July 5, 2018.
24. Wu J, Dong ZY, Ding LX, Liu HL. Influenza Vaccination Practice in Beijing during 1999~2004. *J of pub health and Prev Med* 2005; **16**(4): 19-21.
25. Population Census Office under the State Council & Department of Population and Employment Statistics National Bureau of Statistics of China: Tabulation on the 2010 Population Census of the People's Republic of China. http://www.stats.gov.cn/tjsj/pcsj/rkpc/6rp/indexch.htm. Accessed on January 12, 2015.
26. World Health Organization. WHO interim global epidemiological surveillance standards for influenza (July 2012). http://www.who.int/influenza/resources/documents/INFSURVMANUAL.pdf. Accessed on May 4, 2014.
27. China Health and Retirement Longitudinal Study. http://charls.ccer.edu.cn/en. Acceseed on November 20, 2015.
28. Zhao Y, Hu Y, Smith JP, Strauss J, G. Y. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). *International journal of epidemiology* 2014; **43**(1): 61-8.
29. Feng L, Feng S, Chen T, Yang J, Lau Y, Peng Z, et al. Burden of influenza associated outpatient consultations in China, 2006-2015: a population-based study. Vaccine (Under review).
30. Mertz D, Kim TH, Johnstone J, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. *BMJ* 2013; **347**: f5061.
31. Gao LX. Survey on the Knowledge, Attitudes, Practices of the Public during the Pandemic of A/H1N1 2009 (Dissertation)(in Chinese). 2011.
32. National Health and Family Planning Commission of China: China Health and Family Planning Statistical Yearbook 2018. Chinese Academy of Medical Sciences & Peking Union Medical College Press. Beijing, 2018.
33. Yang J, Jit M, Leung KS, et al. The economic burden of influenza-associated outpatient visits and hospitalizations in China: a retrospective survey. *Infect Dis Poverty* 2015; **4**: 44.
34. Koopmanschap MA, Rutten FF, van Ineveld BM, L. vR. The friction cost method for measuring indirect costs of disease. *J Health Econ* 1995; **14**(2): 171-89.
35. Zhu JL, Mao XM. Research on calculation and analysis of recruitment cost in a tertiary hospital. *Chinese Hospitals* 2012; **16**(12): 63-5.
36. China National Committee on Ageing. The fourth sampling survey on the living conditions of the

elderly in urban and rural China. http://www.cncaprc.gov.cn/contents/2/177118.html. Accessed on December 3, 2018.

37. National Bureau of Statistics of China. Consumer Price Index http://data.stats.gov.cn/english/easyquery.htm?cn=C01. Accessed on Janunary 2, 2016

38. Yang J, Jit M, Zheng Y, et al. The impact of influenza on the health related quality of life in China: an EQ-5D survey. *BMC Infect Dis* 2017; **17**(1): 686.

39. You X, Zhang Y, Zeng J, et al. Disparity of the Chinese elderly's health-related quality of life between urban and rural areas: a mediation analysis. *BMJ open* 2019; **9**(1): e024080.

40. World Health Organization. WHO methods for life expectancy and healthy life expectancy. http://www.who.int/healthinfo/statistics/LT_method.pdf?ua=1&ua=1. Accessed on Janunary 2, 2016.

41. World Health Organization. Making choices in health: WHO guide to cost-effectiveness analysis. In: Tan-Torres Edejer T BR, Adam T, Hutubessy T, Acharya A, Evans DB, Murray CJL., editor.; 2003.

42. Darvishian M, Bijlsma MJ, Hak E, ER. vdH. Effectiveness of seasonal influenza vaccine in community-dwelling elderly people: a meta-analysis of test-negative design case-control studies. *The Lancet Infectious diseases* 2014; **14**(12): 1228-39.

43. Chinese Center for Disease Control and Prevention. Guideline on seasonal influenza vaccination during the 2018–2019 season in China (in Chinese). http://www.chinacdc.cn/jkzt/crb/bl/lxxgm/jszl_2251/201809/t20180921_194050.html. Accessed on October 12, 2018.

44. Ochalek J, Lomas J, Claxton K. Estimating health opportunity costs in low-income and middle-income countries: a novel approach and evidence from cross-country data. *BMJ global health* 2018; **3**(6): e000964.

45. WHO guide for standardization of economic evaluations of immunization programmes, 2nd edition. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

46. Zhou M, Qu S, Zhao L, Kong N, Campy KS, Wang S. Trust collapse caused by the Changsheng vaccine crisis in China. *Vaccine* 2019; **37**(26): 3419-25.

47. Chinadaily: WHO says list of free vaccines should be expanded. http://africa.chinadaily.com.cn/china/2016-03/30/content_24171305.htm. Accessed on May 17, 2016.

48. Zheng Y, Rodewald L, Yang J, et al. The landscape of vaccines in China: history, classification, supply, and price. *BMC Infect Dis* 2018; **18**(1): 502.

49. Chen C, Liu GE, Wang MJ, et al. Cost-effective analysis of seasonal influenza vaccine in elderly Chinese population. *Chin J Prev Med* 2019; **53**(10): 993-9.

Fig1

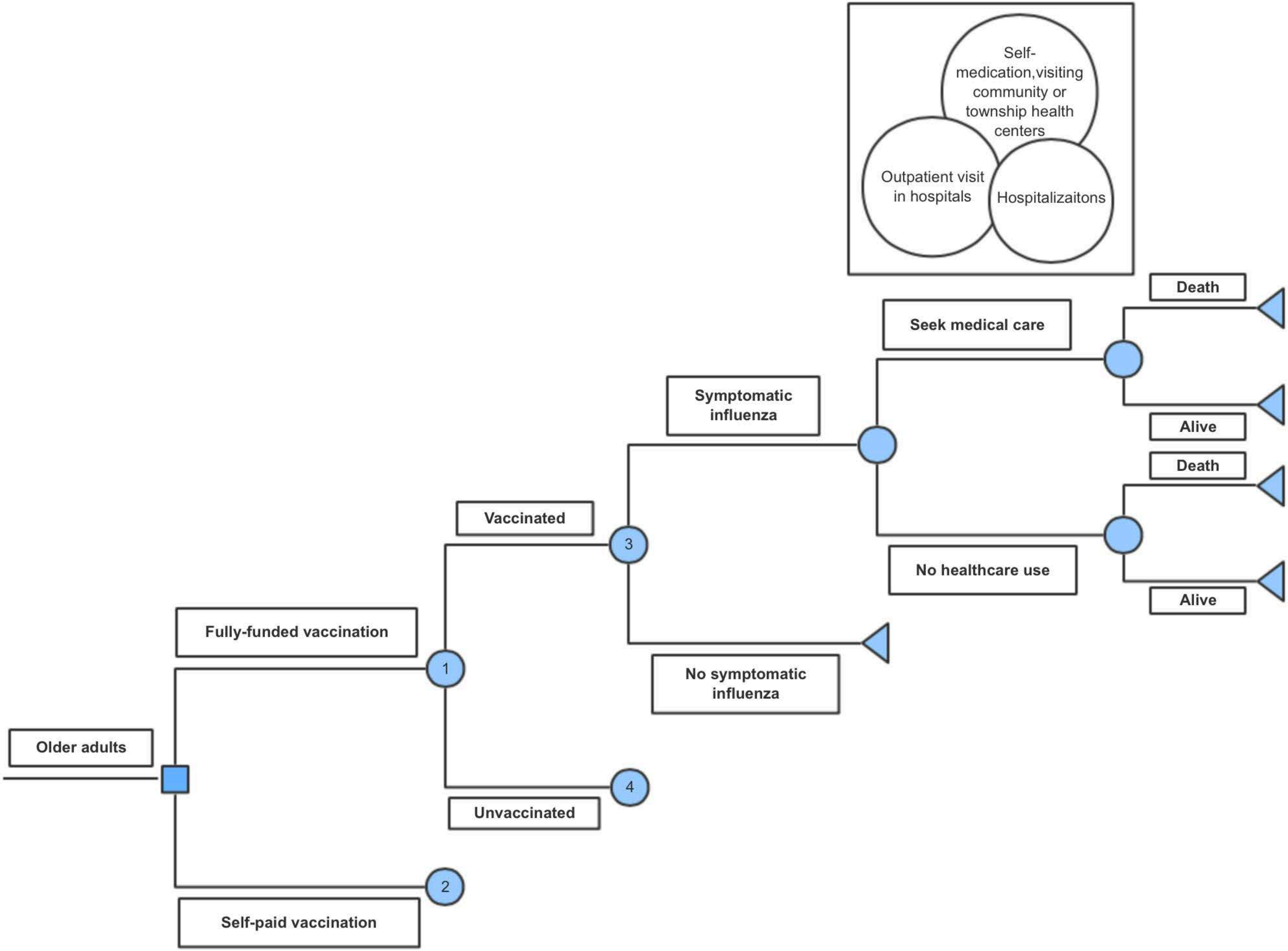
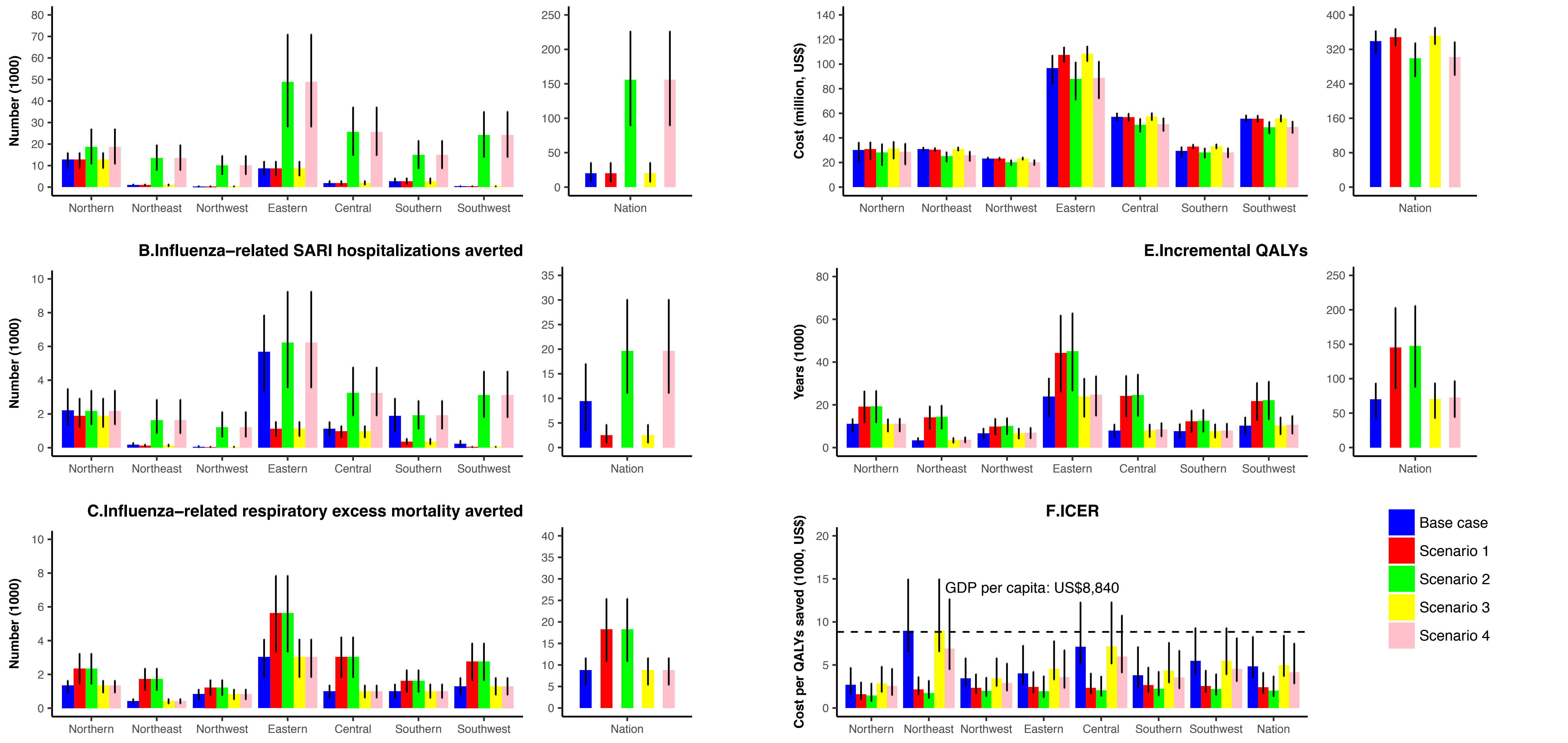

Self-medication,visiting community or township health centers
Outpatient visit in hospitals
Hospitalizaitons
Death
Seek medical care
Symptomatic influenza
Alive
Death
Vaccinated
3
No healthcare use
Alive
Fully-funded vaccination
1
No symptomatic influenza
Older adults
4
Unvaccinated
2
Self-paid vaccination

Fig2



A.Influenza–related ILI consultations averted
Number (1000)
Northern
Northeast
Northwest
Eastern
Central
Southern
Southwest
Nation
B.Influenza–related SARI hospitalizations averted
C.Influenza–related respiratory excess mortality averted
D.Incremental cost
Cost (million, US$)
E.Incremental QALYs
Years (1000)
F.ICER
Cost per QALYs saved (1000, US$)
GDP per capita: US$8,840
Base case
Scenario 1
Scenario 2
Scenario 3
Scenario 4

Fig3

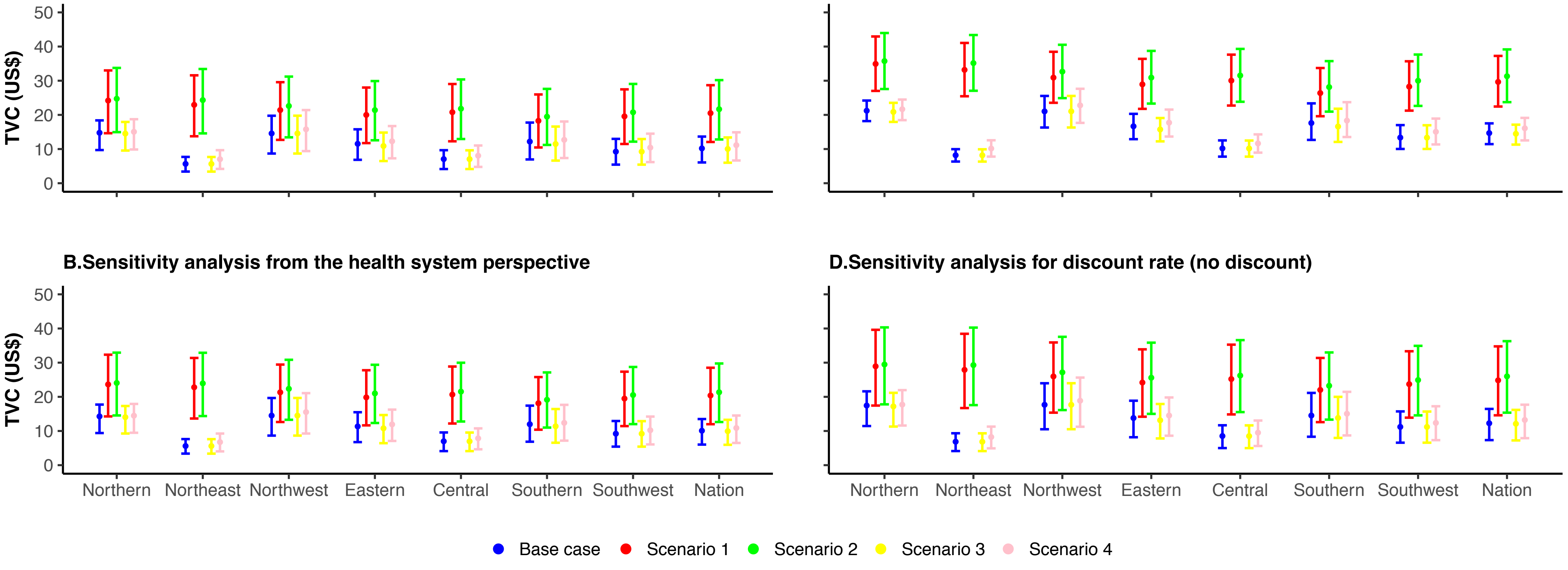
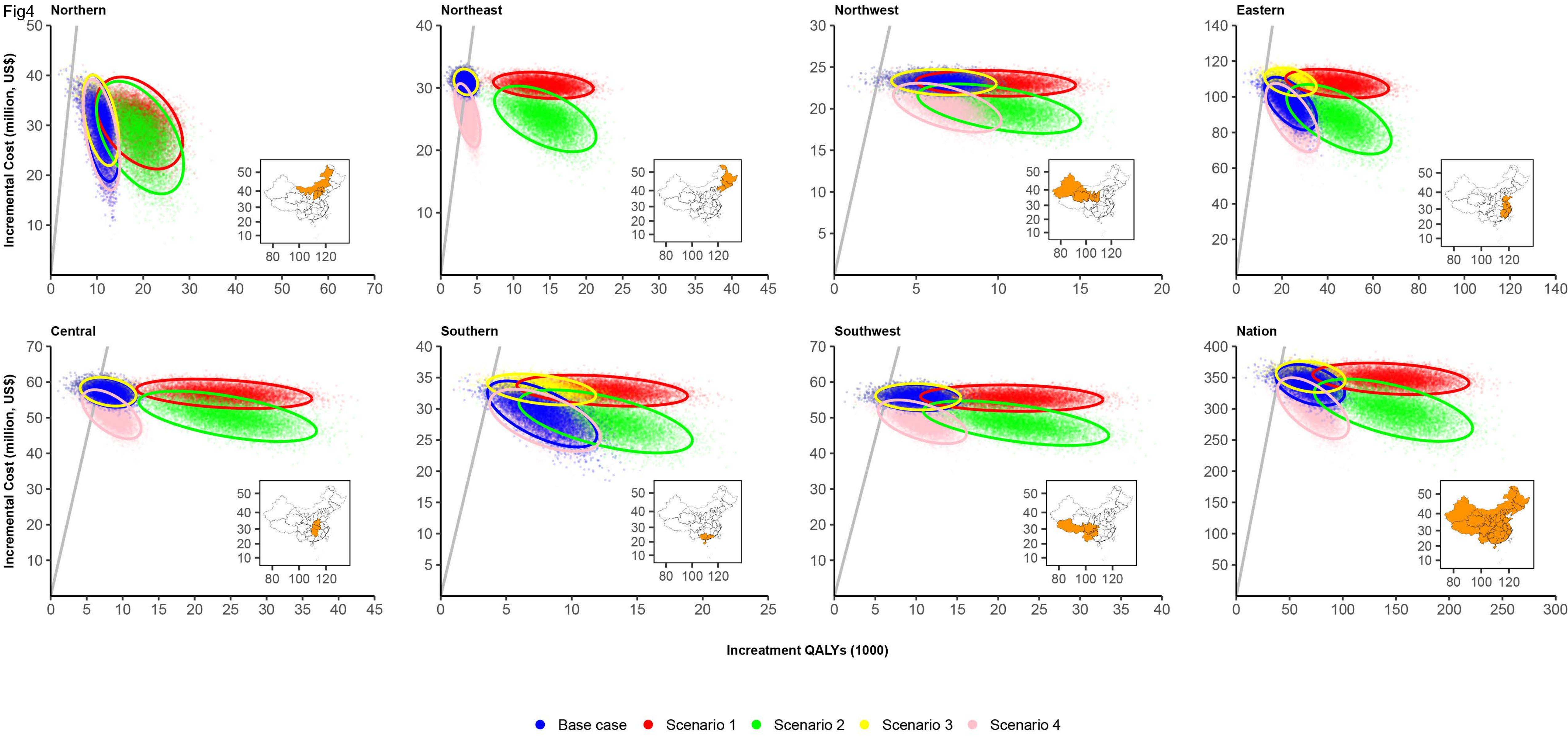

A.Baseline analysis from the societal perspective
B.Sensitivity analysis from the health system perspective
C.Sensitivity analysis for vaccine effectiveness (vaccine match)
D.Sensitivity analysis for discount rate (no discount)
TVC (US$)
0
10
20
30
40
50
Northern
Northeast
Northwest
Eastern
Central
Southern
Southwest
Nation
Base case
Scenario 1
Scenario 2
Scenario 3
Scenario 4

Fig4



Northern
Northeast
Northwest
Eastern
Central
Southern
Southwest
Nation
Incremental Cost (million, US$)
Increatment QALYs (1000)
Base case
Scenario 1
Scenario 2
Scenario 3
Scenario 4