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Parental preference for influenza vaccine for children in China: A discrete choice experiment

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Title: Parental preference for influenza vaccine for children in China: A discrete choice experiment

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ABSTRACT:

Objectives: To explore factors that influenced parents' preferences on influenza vaccination for their children and investigate whether there exists preference heterogeneity among respondents in China.

Design: Cross-sectional study. A discrete choice experiment was conducted and 5 attributes were identified based on literature review and qualitative interviews. A D-efficiency design was developed using Ngene Software.

Setting: Multistage sampling design was used. According to geographical location and the level of economic development, ten provinces in China were selected, and the survey was conducted at community healthcare centers or stations.

Participants: Parents with at least one child aged between 6 months and 5 years old were recruited and the survey was conducted via a face-to-face interview in 2019. In total, 600 parents completed the survey, and 449 who passed the internal consistency test were included for the main analysis.

Main Outcomes and Measures: A mixed logit model was used to analyze the choice experiment data and vaccine preferences. In addition, sociodemographic characteristics were included to explore the preference heterogeneity.

Results: On average respondents preferred to vaccinate for their children. All attributes were statistically significant and among them, the risk of a severe side effect was the most important attribute, followed by the protection rate and duration of vaccine-induced protection. Contrary to our initial expectation, respondents have a stronger preference for the domestic than the imported vaccine. Some preference heterogeneity among parents was also found and in particular, parents who were older, or got high education placed a higher weight on a higher protection rate.

Conclusion: Vaccination safety and vaccine effectiveness are the two most important characteristics that influenced parents' decision to vaccinate against influenza for their children in China. Results

from this study will facilitate future policy implementations to improve vaccination uptake rates.

Key Words: discrete choice experiment, influenza vaccine, children, parental preference, China

Strengths and limitations of this study:

- This is the first study to explore parental preference for influenza vaccine delivery using DCEs in mainland China.
- We recruited participants nationwide, who were more representative to generalize the conclusions.
- The external validity of DCE results cannot be testified, which was similar to most DCE studies.
- We did not differentiate barriers and facilitators among factors associated with vaccine.

1. Introduction

Influenza is an acute respiratory infection caused by influenza viruses and can result in substantial mortality [1]. Among 4 types of influenza viruses, influenza A and influenza B can create epidemics [2]. According to the World Health Organization (WHO), annual epidemics of influenza can lead to 3 to 5 million cases of severe illness and about 290,000 to 650,000 respiratory deaths worldwide [2]. In China, up to 88,000 seasonal influenza-associated respiratory excess deaths occurred each year, accounting for 8.2% of deaths from respiratory diseases [3]. All age groups can be affected by influenza, however, the prevalence of influenza among children under 48 months was highest (up to 33%) [4]. In central China, children under 5 years old accounted for 69% of inpatients owing to influenza-associated severe acute respiratory infections [5]. The economic burden of influenza-associated outpatient and inpatient health care utilization is substantial in China, particularly for young children [6 7].

It is cost-effective or cost-saving to vaccinate against influenza [8 9]. In China, two types of influenza vaccines have been licensed, including trivalent inactivated influenza vaccine (IIV) and tetravalent IIV; whereas the live attenuated influenza vaccine (LAIV) has not been approved [10]. Compared with some European countries, e.g., the Netherlands and the United Kingdom have achieved 82.6% and 72.5% influenza vaccination rate respectively for the elderly in 2008 [11], the average national coverage in China is unexpectedly low and just about 2% for the entire population[12]. In addition, the uptake varied dramatically in groups and regions in China. For example, 0.2% of pregnant women in Suzhou reported influenza vaccination within the last 12 months[13] and the coverage rate among adults in Beijing was 20.6% during the 2014/2015 influenza season[14]. Even in Shanghai, influenza vaccine coverage was highest among children and was just 26.6%[15].

Identifying facilitators and barriers to influenza vaccination would be important to promote vaccination. A systematic review revealed that several facilitators for parents to accept influenza vaccination were belief in vaccine efficacy and influenza severity and susceptibility, perception of advantages of the school setting, and trust in vaccines[16]. In China, the barriers were complex. One study surveyed various populations found that the most common reason for being unvaccinated influenza vaccine was worrying about the side effects[15]. Another study targeted at quadrivalent influenza vaccine for school-aged children showed that the pivotal barriers hindering parents from having their children vaccinated were fear of side effect and no perceived susceptibility[17]. On the contrary, one study indicated perceived severity and knowledge about influenza were not independently significantly associated with uptake[18].

Children aged 6-59 months, recommended routine influenza vaccination strongly by WHO[2], are also among the priority vaccination groups stated by the Chinese Center for Disease Control and Prevention (CDC) [10]. However, the influenza vaccine for children has not been covered by China's National Immunization Program. The decision to vaccinate against influenza for children mostly depends on parents' views and preferences. Consequently, it is crucial to understand what factors can influence parents' vaccination decisions to facilitate more effective policy implementation.

This study employed a discrete choice experiment (DCE), a stated preference elicitation method based on random utility theory, to explore parental preference for influenza vaccines. DCEs have been widely used to estimate preference for vaccines [19], such as human papillomavirus, influenza, and hypothetical vaccines [20-22]. Although there exist some DCE studies on vaccines in China, respondents normally came from one particular province [23 24]. This is the first DCE study on vaccination that aims to recruit respondents nationwide by involving parents from ten provinces to

understand the preference of influenza vaccination. This study aimed to address two research questions: i) to elicit the preference of parents when choosing influenza vaccine for their children; ii) to investigate whether there exists preference heterogeneity among respondents.

2. Methods

Discrete choice experiments are increasingly used in health economics to identify and evaluate the participants' preferences [25]. DCEs can also be used to estimate participants' willingness to pay as well as to predict program uptake rates given a set of goods or services characteristics [26 27]. In the DCE, a vaccine profile can be described by a series of attributes and their corresponding levels, and under the random utility theory, respondents choose the option with the highest utility from the alternatives presented [28]. The DCE design and analysis were conducted following the checklist and reports of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Conjoint Analysis Task Forces [29-31].

2.1 Survey design

Based on previously published literature [19 21 32], twelve attributes were identified initially. To assess the appropriateness of attributes and levels included and to further narrow down the number of attributes, four experts on vaccination were interviewed face-to-face in Jinan Maternity and Childcare Hospital. Two focus groups (n=12) were also conducted. One focus group included four parents only, and the other contained one vaccinologist, three parents, and four health economics/DCE experts. They were asked to review and rank the list of attributes. Finally, five attributes were selected for this study (Table 1).

[Table 1]

A D-efficient design was developed using Ngene Software (www.choice-metrics.com), which

yielded 60 choice sets that were further divided into six blocks to reduce respondents' cognitive burden. To check for internal consistency, one choice set in each block was duplicated, which was excluded in the analysis. Each respondent received one block randomly and was asked to answer 11 choice sets. For those who failed the consistency test, their data were excluded from the main analysis. Before completing DCE questions, respondents were also asked to rate the importance of five attributes.

Given the decision to vaccinate is a voluntary decision, instead of directly adding an opt-out option, a two-stage response DCE design was used to maximize the information gained from the respondents [33]. In the first stage, the respondents were forced to choose between two hypothetical vaccination profiles. Then, they were asked to confirm whether they would vaccinate their preferred option from the first stage for their children.

In addition to DCE questions (which were presented in a hardcopy questionnaire), socio-demographic characteristics of respondents and their children were collected using an iPad. A pilot was conducted among 15 parents in Beijing and Jinan in July 2019 to examine the acceptability, comprehensibility, and validity. A few modifications were implemented based on the feedback from the pilot. An example of a final choice set was shown in Figure 1.

[Figure 1]

2.2 Study population and data collection

To ascertain national parental values and preference for influenza vaccines, the survey used a multistage sampling design. First, ten provinces/municipalities were selected based on the Division of Central and Local Financial Governance and Expenditure Responsibilities in the Healthcare Sector released by the State Council in 2018, which divided 31 provinces/municipalities in mainland China

into five layers. According to geographical location and the level of economic development, ten provinces/municipalities represented eastern region (Shandong and Shanghai), western region (Gansu and Chongqing), southern region (Yunnan and Guangdong), northern region (Beijing and Jilin), middle region (Henan and Jiangxi), which were shown in Figure 2. Next, except for three municipalities (Beijing, Shanghai, and Chongqing), in each of the other seven provinces, one provincial capital, and one non-provincial-capital city were chosen. Finally, the parents with at least one child aged 6 months and 5 years old were recruited from community healthcare centers or stations, which were the main provider of vaccination service.

[Figure 2]

According to a rule of thumb suggested by Orme [34], a sample size of 75 (500*3/2*10=75) would be desirable for the main effects model based on the number of analysis cells, alternatives and choice sets. We aimed to recruit a minimum of 100 respondents in each region [27 35]. Hence, we intended to survey 60 parents in each province and 120 parents in each region.

The anonymous survey was administered between August and October 2019. Data was collected by one-on-one face-to-face interviews from parents waiting for routine vaccination for their children or remaining for observation after routine vaccination. The vaccination rates for routine vaccines, such as DTaP, HepB, were more than 95% in China [36], so the sample bias for participants recruited from the vaccination sites was very limited. Before enrolling in the survey, respondents were informed about the survey purpose and content by interviewers who have been trained by the research team. Electronic written consent was obtained from all respondents. The study received ethical approval from the Peking University Institutional Review Board (IRB00001052-19076).

2.3 Statistical analysis

Responses to the hardcopy DCE questionnaire were double-entered into a database set up by the EpiData 3.1 software and then matched with other socio-demographic characteristics obtained from the iPad for statistical analyses. In cases where the number of missing DCE responses was more than two tasks or the majority of socio-demographic data missed, respondents were excluded from the final analysis.

A mixed logit model was employed to analyze DCE data which takes into account potential preference heterogeneity [37]. The utility function can be written as below:

$$U_{ijt} = X_{ijt}\beta + \varepsilon_{ijt}$$

Where U_{ijt} is the utility that respondent i derives from choosing alternative j in the choice set t, X_{ijt} is a vector representing the levels of the attributes, β is a vector of coefficients corresponding to attribute levels, and ε_{ijt} is a random error term. The cost attribute was treated as a continuous variable, while other attributes were dummy coded. In a mixed logit model, coefficients of attribute levels are commonly assumed to follow a normal distribution to account for preference heterogeneity, i.e., β is composed of a mean coefficient as well as a standard deviation. A significant positive (negative) coefficient represents a positive (negative) preference for an attribute level. The importance of attribute can be calculated through the difference of level coefficients in the same attribute. Therefore, the relative importance of attributes can be estimated by comparing the utility range of each attribute [38].

We further examined whether the elicited preferences varied by particular socio-demographic characteristics. Finally, vaccination update rates were predicted to facilitate the interpretation of DCE results to decision-makers. Descriptive analyses including Student's test, χ^2 test, and Wilcoxon rank-

sum test were adopted to compare means and proportions between subgroups, respectively. All statistical analyses were conducted using Stata 12.1 software. The mixed models were estimated by simulated maximum likelihood using the Stata command developed by Hole[39] and 2000 random draws were used to achieve stability.

2.4 Patient and public involvement

The study did not involve the patients. The public was involved at the stage of questionnaire design, pretesting, and feedback from respondents was incorporated into questionnaire revisions.

3. Results

A total of 600 parents consented and participated in the survey. Among them, 3 and 18 parents were excluded from the analysis due to missing of socio-demographic information and failure in completing the majority of DCE questions, respectively. Among the remaining 579 parents, they had a mean age of 31 years old, most (79%) of them are mothers of children, and the mean age of their children was 2 years old. At the time of the survey, 355 (61%) parents were working and 337 (58%) had at least two children. Among DCE responses, 449 (78%) respondents passed the consistent test (i.e., duplicated task) and they were treated as the main study sample. There was no significant difference in socio-demographic characteristics between those who passed and who failed the consistent test except for region (urban vs rural). More details on respondents' socio-demographic characteristics are presented in Table 2.

[Table 2]

3.1 Importance rating

Figure 3 showed the relative importance of five DCE attributes ranked by respondents prior to the

pairwise choice tasks. The most important attribute was the protection rate followed by the risk of severe side effect event, whereas the out-of-pocket cost of the vaccine and duration of vaccine-induced protection were less important.

[Figure 3]

3.2 Discrete choice experiment results

The DCE results incorporating the second-stage choices and based on the main study sample are reported in Table 3. As a sensitivity analysis, the full sample analysis results are shown in Table S1 whilst the analyses on forced-choice responses from the main study sample are presented in Table S2. All attributes were statistically significant. Overall, similar patterns can be seen from the supplementary material.

Focusing on Table 3, the mixed logit model estimates suggested that the higher the protection rate, the longer the duration of vaccine-induced protection, the lower the risk of severe side effect, the lower the cost, the more likely that parents would be willing to vaccine for their children. Contrary to our initial hypothesis, respondents prefer domestic rather than imported vaccination. Most estimated standard deviations were significant, indicating the existence of preference heterogeneity among parents.

The vaccine with the lowest risk of severe side effects had the highest preference weight when compared with a relatively high risk of severe side effects, followed by the highest protection rate. And the duration of vaccine-induced protection was less important. Reducing the risk of severe side effects from high to low could yield 4.4(2.626/0.596) times as much as utilities increasing the duration of vaccine-induced protection from 6 months to 12 months.

The coefficient of non-vaccination was significantly negative, indicating that on average the

parents were more likely to vaccinate their children against influenza regardless of the vaccine profile described by attributes and levels.

[Table 3]

To evaluate whether there was a significant difference between parents with various characteristics, a series of interaction terms between respondents' characteristics and attribute levels were explored and the result was reported in Table 4. We found that parents who were beyond 30 years old or lived in urban were more likely to choose vaccination. Highly educated, those beyond 30 years old and those who lived in rural areas placed a higher weight on the highest protection rate. And Those who lived in rural areas also had stronger preference for the lowest risk of severe side effect. Other than what has been reported, we found no significant influence between attribute levels and the working status of parents and the gender of children.

[Table 4]

3.3 Predicted uptake rates for different scenarios

Figure 4 showed the results of predicted probability when changing a particular attribute level based on results reported in Table 3. Corresponding to the reference within DCE's main effect analysis, the scenario was selected as the baseline presented by 70% protection rate, 6-month duration, high risk of severe side effect, domestic and costing CNY150. For the change within an attribute, the decrease in the risk of serious adverse effects from high to low had the largest effect on preference for influenza vaccines, in which the probability of taking that vaccination increased by 86%. For the changes with multiple attributes, the vaccine with 80% protection rate was preferred to free one with 12-month duration. On the other hand, the impact of cost and duration change was small. The most attractive vaccine was '⑤+⑥' one, which has the lowest risk of severe side effect and the highest protection rate.

[Figure 4]

4. Discussion

This study has estimated parental preference for vaccinating against influenza for their children. To the best of our knowledge, this is the first study to explore parental preference for influenza vaccine delivery using DCEs in mainland China. A previous DCE study conducted in Hong Kong Special Administrative Region surveyed the adult to assess the relative effects of different factors for influenza vaccination choices [40]. This is also the first DCE study on vaccination that recruits respondents nationwide to achieve a more representative result.

We found that on average respondents from this study preferred vaccination against influenza for their children from the hypothetical vaccination scenarios, which is consistent with other DCE study findings [32 41]. The relatively high acceptance was also documented in another survey that aimed to study the knowledge, attitudes, and practices towards the influenza vaccine among young workers in China [42].

In general, all the attributes included in our study were statistically significant and preference heterogeneity existed among both observable and non-observable personal characteristics. Among all the attributes, the risk of severe side effects and protection rate of the vaccine were the top two most important characteristics perceived by parents. Their important roles in the choice for vaccination are in line with other influenza vaccine DCE studies [21 32]. Similar findings have also been reported in other vaccines. A DCE study surveying girls' preference for HPV vaccination reported that respondents preferred low severe side effects [43] and other studies found willingness to vaccinate was closely related to vaccine safety and efficacy [41 44]. The above findings could suggest that to reduce the risk of severe side effects and to increase vaccine effectiveness could be regarded as two universal

procedures to effectively achieve higher vaccination coverage.

Somewhat surprising, given the recent Changchun Changsheng vaccine incident, this study found that parents preferred the domestic vaccine to the imported vaccine. However, the same finding was also reported in one recent DCE study conducted in Shanghai, even though there are substantial differences, e.g., study population [24]. One potential reason for which domestic vaccine was preferred may be that it is thought to be more effective [45] and more accessible. And the other is that regulatory environment is more stringent. Indeed, the government facilitated a public consultation after the incident in 2018 [46], and the Standing Committee of the National People's Congress voted to adopt the first Vaccine Administration Act in 2019, which aimed to tighten vaccine regulation [47].

The out-of-pocket cost was found to be less important compared to the other attributes. Based on the calculation of uptake rates, the probability of vaccination was affected slightly by a change in cost. This differs from some previous studies in which cost was found to be an important factor driving preferences [22 38 48]. The above results were incomparable for our study due to differences in targeted vaccines. In reality, the out-of-pocket cost of the influenza vaccine is affordable when comparing to the household income. For example, the highest out-of-pocket cost of the influenza vaccine made up about 1% of monthly income in our study. Furthermore, most families in China are willing to spend more for their children [49], and cost is not a key factor.

When studying the preference heterogeneity, the protection rate has again stood out as a key attribute that those who were older, lived in a rural area or got higher education all placed a higher weight on a higher protection rate. By far influenza vaccine has not been included in the national immunization program schedule in China and to improve the vaccination rate in particular for people mentioned above, providing more information about as well as improving the safety and effectiveness

of vaccines will be the most important factor.

The present study had several limitations. Firstly, our study includes 600 respondents recruited from 10 provinces (and among them, 449 was included for the main analysis) which may be not large enough to represent the whole of China. However, we did not find significant regional preference heterogeneity from the analysis. Secondly, though attributes included in our study were identified and selected through previous literature, interview with experts, and focus group discussion, following the recommended procedure, we cannot guarantee that all attributes concerned with parental vaccination choice were included. Thirdly, we did not differentiate barriers and facilitators among factors associated with vaccine, it may be more useful to distinguish barriers and facilitators. Finally, similar to most DCE studies, the external validity of DCE results cannot be testified. Nevertheless, the consistency test and importance rating were implemented to confirm DCE's internal validity.

5. Conclusion

Vaccinating influenza vaccines is the most effective measure to prevent the prevalence of influenza. Although WHO and the Chinese CDC have recommended the influenza vaccine to the whole population, especially the youth, the vaccination rate is extremely low. This study aimed to investigated national parents' preference for vaccinating against influenza for their children based on a nationwide sample. Based on a discrete choice experiment, the study showed that on average parents were more willing to vaccinate their children. Among five attributes been examined, the risk of severe side effects and protection rate were key drivers of preference among parents in China, and preference heterogeneity was found among parents. The findings from this study will shed light on future policy implementation to improve the influenza vaccination rate in China.

Contributorship statement:

Conceptualization: Shunping Li, Hai Fang.

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Formal analysis: Tiantian Gong, Ping Liu.

Funding acquisition: Hai Fang.

Methodology: Gang Chen, Tiantian Gong, Ping Liu.

Project administration: Shunping Li, Gang Chen.

Supervision: Shunping Li, Hai Fang.

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Writing-review & editing: Shunping Li, Tiantian Gong, Gang Chen, Ping Liu, Xiaozhen Lai, Hongguo Rong, Xiaochen Ma, Zhiyuan Hou, Hai Fang.

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Figure titles and footnotes

Fig.1 An example of discrete choice question (translated version)

Fig.2 Provinces/municipalities selected in China

Fig.3 Importance Rating of Attributes

Fig.4 Simulated probabilities for influenza vaccination under change of a single attribute.

Notes: The baseline was presented by a 70% protection rate, 6-month duration, high risk of severe side effect, domestic and costing CNY150.

Table 1 Attributes and attributes levels for DCE choice questions

Attributes	Attributes levels		Explanation
Protection rate prevented by a vaccine	1	70%	The percentage of children that will be protected against an influenza infection when vaccinated.
	2	80%	
	3	90%	
Duration of vaccine-induced protection	1	6 months	The number of months that the vaccine protects against influenza.
	2	12 months	
The risk of serious side effect	1	1/100,000	The number of vaccinated children that will suffer from serious adverse events due to vaccination. Serious adverse events included hospitalization or prolongation of hospitalization, persistent or significant disability or incapacity.
	2	2/100,000	
	3	10/100,000	
Location of vaccine manufacturer	1	domestic	The vaccine manufacturers were divided into Chinese-made (domestic) and foreign (imported) categories
	2	imported	
The out-of-pocket cost of a vaccine	1	0 Yuan	The parents may have to pay of the vaccine cost out-of-pocket.
	2	75 Yuan	
	3	150 Yuan	

Table 2 Socio-demographic characteristics of the study population

	All (N=579)		Parents who passed the consistency test		Parents who failed the consistency test		P-value
	Mean	SD	Mean	SD	Mean	SD	
Age(years)	31.07	0.21	31.20	0.25	30.59	0.42	0.231 [a]
Household size	4.60	0.05	4.57	0.06	4.73	0.12	0.194 [a]
Monthly income(RMB)	11988.4	482.04	12025.66	480.81	11860	1365.26	0.886 [a]
Monthly expenditure(RMB)	6796.17	250.81	6894.88	274.26	6455.23	593.19	0.465 [a]
Child' age	2.00	0.05	2.02	0.06	1.93	0.11	0.462 [a]
	N	%	N	%	N	%	
Relation							
Mother	459	79.27	354	78.84	105	80.77	0.633 [b]
Father	120	20.73	95	21.16	25	19.23	
Ethnic							
Han	534	92.23	414	92.20	120	92.31	0.969 [b]
Minority	45	7.77	35	7.80	10	7.69	
Child gender							
Male	294	50.78	220	49.00	74	56.92	0.111 [b]
Female	285	49.22	229	51.00	56	43.08	
One child							
Yes	242	41.80	189	42.09	53	40.77	0.787 [b]
No	337	58.20	260	57.91	77	59.23	
Child health							
Very good	278	48.01	219	48.78	59	45.38	0.415 [c]
Good	224	38.69	173	38.53	51	39.23	
Fair or poor	77	13.3	57	12.69	20	15.38	
Job							
Working	355	61.31	278	61.92	77	59.23	0.580 [b]
Non-working	224	38.69	171	37.86	53	40.77	
Region							
Urban	357	61.66	288	64.14	69	53.08	0.022 [b]
Rural	222	38.34	161	35.86	61	46.92	
Education level							
Senior and below	211	53.71	234	52.12	77	59.23	0.152 [b]
College and above	268	46.29	215	47.88	53	40.77	

Note:

1.a-Student's test, b-χ^2 test, c-Wilcoxon rank-sum test.

Table 3. Mixed logit model results with only main effects

Attributes	β	SE	P-value	SD	SE	P-value
Non-vaccination	-5.236	0.757	<0.001	6.391	0.586	<0.001
Protection rate prevented by a vaccine (ref:70%)						
80%	0.935	0.089	<0.001	0.310	0.229	0.175
90%	1.921	0.133	<0.001	1.436	0.140	<0.001
Risk of serious side effect event (ref:10/100,000)						
2/100,000	1.795	0.116	<0.001	0.875	0.152	<0.001
1/100,000	2.626	0.158	<0.001	1.754	0.157	<0.001
Location of vaccine manufacturer (ref: domestic)						
Imported	-0.319	0.082	<0.001	1.181	0.105	<0.001
Duration of vaccine-induced protection (ref:6month)						
12 months	0.596	0.067	<0.001	0.571	0.101	<0.001
Cost	-0.002	0.001	0.016	0.011	0.001	<0.001
Log likelihood			-2648.049			
No .of respondents			449			
No. of observations			13446			

Note:

1.β-coefficient, SE-standard error, SD-standard deviation, ref-reference. All attributes except for cost were coded for dummy variables.

2. A total of 600 parents enrolled in the survey and 579 completed the majority of the questionnaire at least. Respondents (449) who passed the consistency test were included in the main DCE result reported in this table.

Table 4 Results of Mixed logit model with main effects and interactions

Attributes	β	SE	P-value	95%CI	
Non-vaccination	-6.178	0.767	<0.001	-7.680	-4.675
Protection rate prevented by a vaccine (ref:70%)					
80%	0.940	0.088	<0.001	0.767	1.113
90%	1.218	0.235	<0.001	0.758	1.679
Risk of serious side effect event (ref:10/100,000)					
2/100,000	1.804	0.116	<0.001	1.576	2.031
1/100,000	2.334	0.265	<0.001	1.815	2.854
Location of vaccine manufacturer (ref: domestic)					
Imported	-0.298	0.079	<0.001	-0.454	-0.143
Duration of vaccine-induced protection(ref:6month)					
12 months	0.583	0.065	<0.001	0.456	0.711
Cost	-0.001	0.002	0.624	-0.005	0.003
Interaction terms					
Non-vaccination * age (>30 years old)	2.843	0.778	<0.001	1.319	4.367
Non-vaccination * rural	-2.216	0.973	0.023	-4.123	-1.305
Non-vaccination * father	-0.157	0.746	0.833	-1.620	-0.302
Non-vaccination *only one child	1.017	0.967	0.293	-0.878	2.911
90% protection rate* age (>30 years old)	0.581	0.209	0.005	0.173	0.990
90% protection rate* rural	0.732	0.220	0.001	0.302	1.163
90% protection rate* education level (college and above)	0.540	0.213	0.011	0.123	0.956
90% protection rate*only one child	-0.231	0.216	0.285	-0.655	0.192
Lowest risk of serious side effect*only one child	-0.506	0.236	0.032	-0.969	-0.043
Lowest risk of serious side effect*rural	0.838	0.240	<0.001	0.367	1.309
Lowest risk of serious side effect* age (>30 years old)	0.372	0.223	0.096	-0.066	0.810
Lowest risk of serious side effect* education level (college and above)	0.291	0.230	0.206	-0.160	0.742
Log likelihood			-2631.978		
No .of respondents			449		
No .of observations			13446		

Note:

1.β-coefficient, SE-standard error, SD-standard deviation, CI-confidence interval, ref-reference. All attributes except for cost were coded for dummy variables.

2. A total of 600 parents enrolled in the survey and 579 completed the majority of the questionnaire at least. Respondents (130) who failed the consistency test were excluded from the main DCE result reported in this table.

3. Interaction terms were treated as fixed effect variables, and the others as random effect variables.

	Influenza vaccine A	Influenza vaccine B
Protection rate prevented by a vaccine	70%	90%
Duration of vaccine-induced protection	12 months	6 months
Risk of severe side effect	2/100,000	1/100,000
Location of vaccine manufacturer	domestic	imported
Out-of-pocket cost of the vaccine	0 Yuan	75 Yuan
Which option would you be more likely to choose?	☐	☐
In reality, would you vaccine your child the option you chose before	☐ Yes ☐ No	

Fig.1 An example of discrete choice question (translated version)

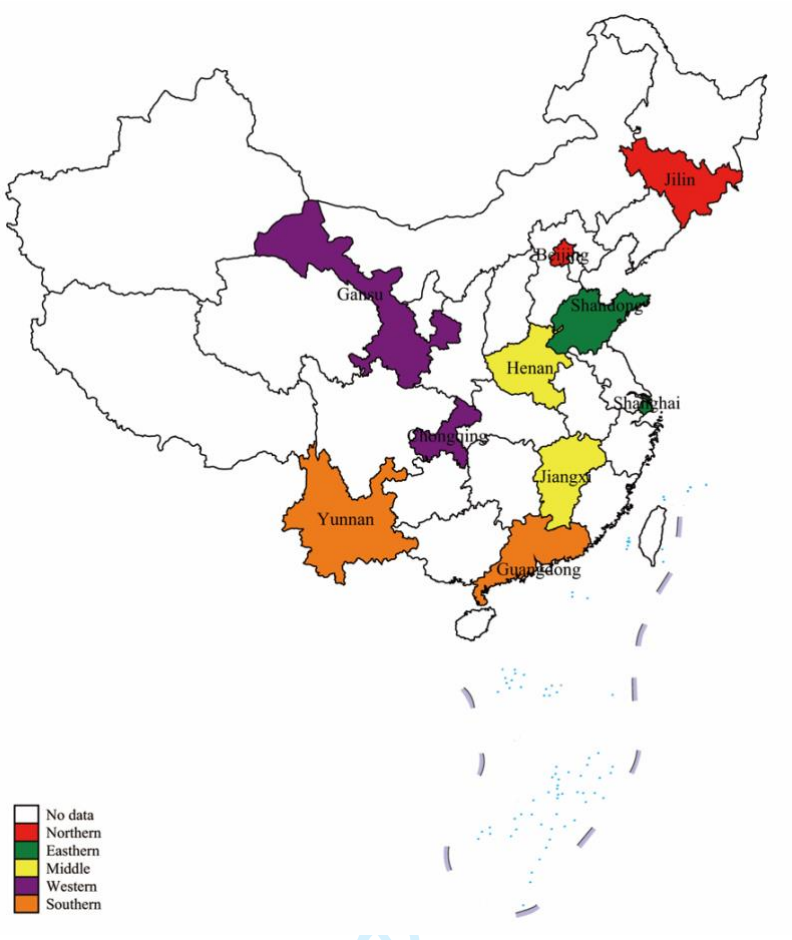

Fig.2 Provinces/municipalities selected in China

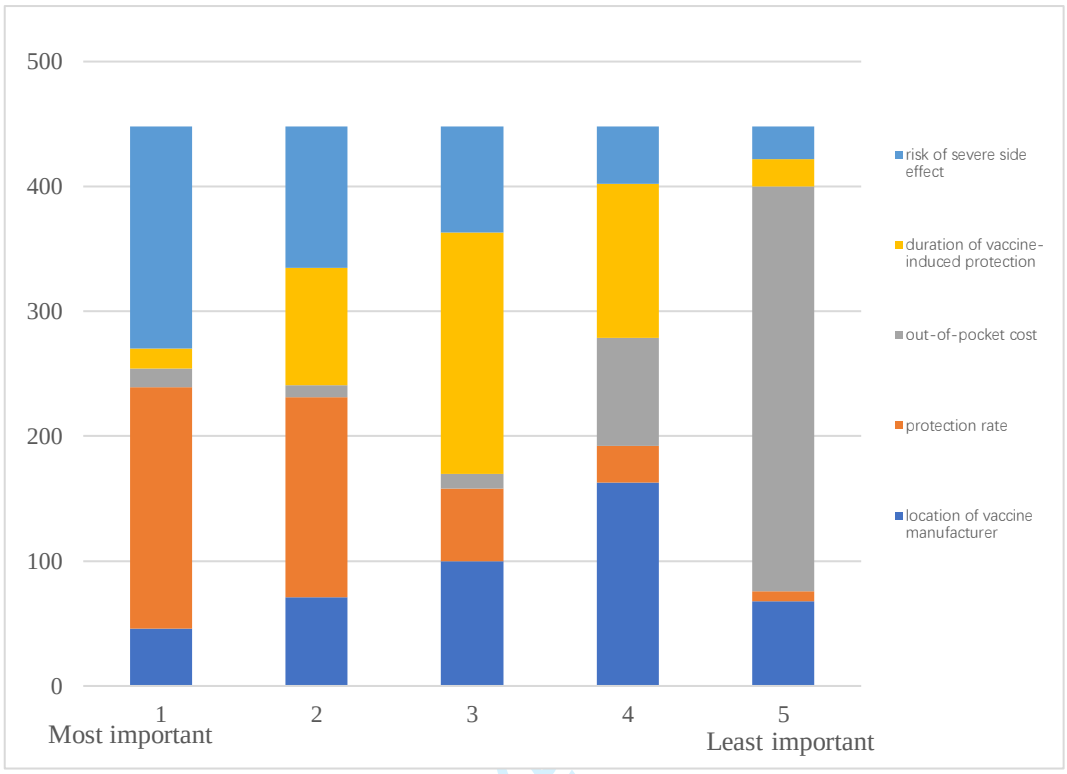

Fig.3 Importance Rating of Attributes

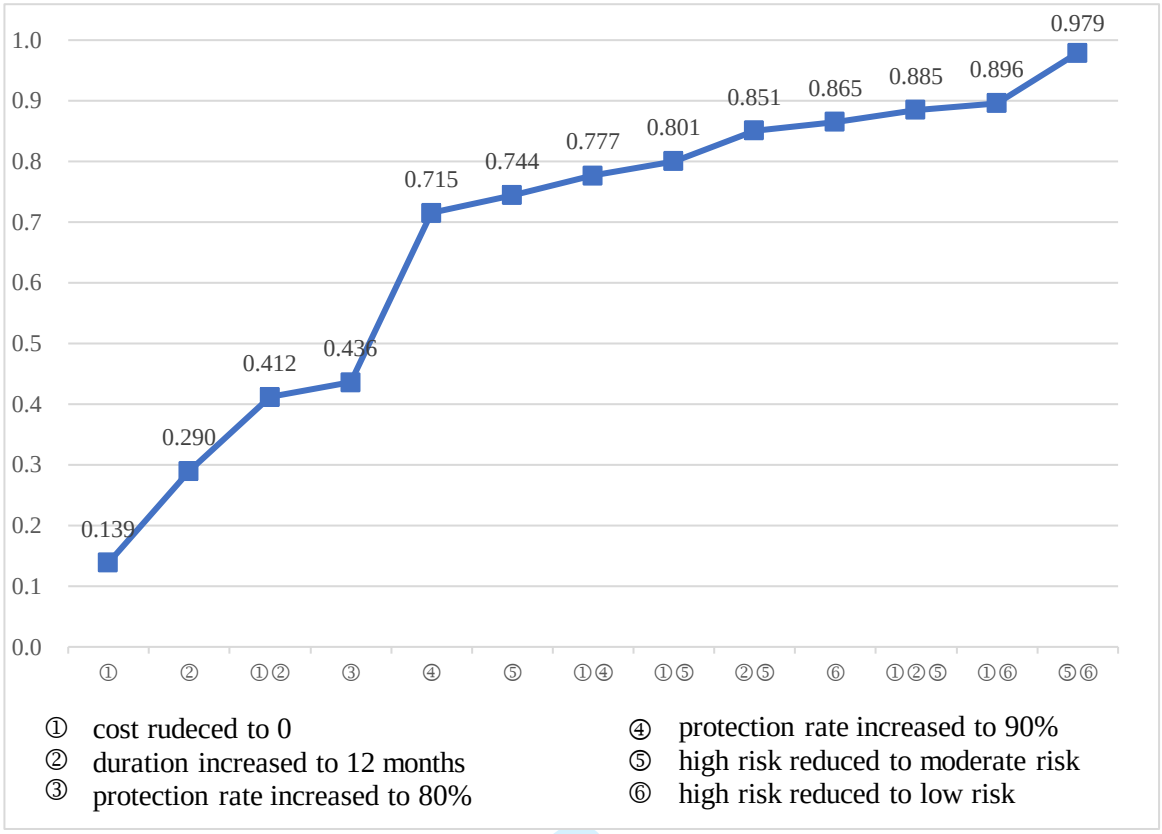

Fig.4 Simulated probabilities for influenza vaccination under change of a single attribute

Notes: The baseline was presented by a 70% protection rate, 6-month duration, high risk of severe side effect, domestic and costing CNY150.

SUPPLEMENTARY MATERIAL

Table S1 Mixed logit model results with only main effects for unforced choice in the full sample

Attributes	β	SE	P-value	SD	SE	P-value
Non-vaccination	-3.487	0.477	<0.001	5.172	0.455	<0.001
Protection rate prevented by a vaccine (ref:70%)						
80%	0.803	0.069	<0.001	0.065	0.303	0.830
90%	1.655	0.099	<0.001	1.187	0.104	<0.001
Risk of severe side effect event (ref:10/100,000)						
2/100,000	1.559	0.089	<0.001	0.794	0.126	<0.001
1/100,000	2.205	0.116	<0.001	1.539	0.124	<0.001
Location of vaccine manufacturer (ref: domestic)						
Imported	-0.257	0.062	<0.001	0.934	0.080	<0.001
Duration of vaccine-induced protection (ref:6month)						
12 months	0.594	0.055	<0.001	0.599	0.090	<0.001
Cost	-0.002	0.001	0.010	0.010	0.001	<0.001
Log likelihood			-3709.407			
Respondents, n			579			
Observations, n			17337			

Note:

1.unforced choice-parents can choose to not vaccinate influenza vaccines for their children and the opt-out choice in the second stage was analyzed in the model.

2.β-coefficient, SE-standard error, SD-standard deviation, ref-reference. All attributes except for cost were coded dummy variables.

3. A total of 600 parents enrolled in the survey and 579 completed the majority of the questionnaire.

Table S2 Mixed logit model results with only main effects for forced-choice data

Attributes	β	SE	P-value	SD	SE	P-value
Protection rate prevented by a vaccine (ref:70%)						
80%	0.794	0.078	<0.001	0.104	0.354	0.769
90%	1.679	0.119	<0.001	1.271	0.128	<0.001
Risk of severe side effect event (ref:10/100,000)						
2/100,000	1.718	0.111	<0.001	0.982	0.141	<0.001
1/100,000	2.558	0.156	<0.001	1.774	0.154	<0.001
Location of vaccine manufacturer (ref: domestic)						
Imported	-0.248	0.072	0.001	1.050	0.093	<0.001
Duration of vaccine-induced protection (ref:6month)						
12 months	0.526	0.060	<0.001	0.520	0.098	<0.001
Cost	-0.001	0.001	0.190	0.010	0.001	<0.001
Log likelihood			-2399.908			
Respondents, n			477			
Observations, n			9538			

Note:

1.forced choice: parents were forced to choose the preferred vaccine from alternatives presented and the choice in the first stage was analyzed in the model.

2.β-coefficient, SE-standard error, SD-standard deviation, ref-reference. All attributes except for cost were coded dummy variables.

3. A total of 600 parents enrolled in the survey and 579 completed the majority of the questionnaire at least. Respondents (477) who passed the consistency test in the first stage were included in the main effects DCE result reported in this table.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*NA*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
Outcome data	15*	Report numbers of outcome events or summary measures	11,12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA

		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11,12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13,14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Parental preference for influenza vaccine for children in China: A discrete choice experiment

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Keywords:	PUBLIC HEALTH, INFECTIOUS DISEASES, PAEDIATRICS

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Title: Parental preference for influenza vaccine for children in China: A discrete choice experiment

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ABSTRACT:

Objectives: To investigate what factors affect parents' influenza vaccination preference for their children and whether there exists preference heterogeneity among respondents in China.

Design: Cross-sectional study. A discrete choice experiment (DCE) was conducted. Five attributes were identified based on literature review and qualitative interviews, including protection rate, duration of vaccine-induced protection, risk of serious side effects, location of manufacturer and out-of-pocket cost.

Setting: Multistage sampling design was used. According to geographical location and the level of economic development, ten provinces in China were selected, and the survey was conducted at community healthcare centers or stations.

Participants: Parents with at least one child aged between 6 months and 5 years old were recruited and the survey was conducted via a face-to-face interview in 2019. In total, 600 parents completed the survey, and 449 who passed the internal consistency test were included in the main analysis.

Main Outcomes and Measures: A mixed logit model was used to estimate factors affecting parents' preference to vaccinate their children. In addition, sociodemographic characteristics were included to explore the preference heterogeneity.

Results: In general, respondents preferred to vaccinate their children. All attributes were statistically significant and among them, the risk of severe side effects was the most important attribute, followed by the protection rate and duration of vaccine-induced protection. Contrary to our initial expectation, respondents have a stronger preference for the domestic than the imported vaccine. Some preference heterogeneity among parents was also found and in particular, parents who were older, or highly educated placed a higher weight on a higher protection rate.

Conclusion: Vaccination safety and vaccine effectiveness are the two most important characteristics

that influenced parents' decision to vaccinate against influenza for their children in China. Results from this study will facilitate future policy implementations to improve vaccination uptake rates.

Key Words: discrete choice experiment, influenza vaccine, children, parental preference, China

Strengths and limitations of this study:

- This is the first nationwide study to explore parental preference for influenza vaccine for their children using DCEs in mainland China.
- The experimental design and data analysis were conducted following the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Conjoint Analysis Task Forces.
- The external validity of DCE results cannot be testified, which is a common limitation of most DCE studies.
- We did not differentiate barriers and facilitators among factors associated with the vaccination decision.

1. Introduction

Influenza is an acute respiratory infection caused by influenza viruses and can result in substantial mortality [1]. Among 4 types of influenza viruses, influenza A and influenza B can create epidemics [2]. According to the World Health Organization (WHO), annual epidemics of influenza can lead to 3 to 5 million cases of severe illness and about 290,000 to 650,000 respiratory deaths worldwide [2]. In China, up to 88,100 seasonal influenza-associated respiratory excess deaths occurred each year from 2010 to 2014, accounting for 8.2% of deaths from respiratory diseases [3]. All age groups can be affected by influenza, however, the prevalence of influenza among children under 48 months was highest (up to 33%) [4]. In central China, children under 5 years old accounted for 69% of inpatients owing to influenza-associated severe acute respiratory infections [5]. The economic burden of influenza-associated outpatient and inpatient health care utilization is substantial in China, particularly for young children [6 7].

It is cost-effective or cost-saving to vaccinate against influenza [8 9]. In China, two types of influenza vaccines have been licensed, including trivalent inactivated influenza vaccine (IIV) and tetravalent IIV; whereas the live attenuated influenza vaccine (LAIV) has not been approved [10]. The vaccination rate in children 6 months to 18 years of age was 49% in the United States during the 2010-2011 flu seasons[11], the vaccination rates in 2010 and 2011 in the Israeli paediatric population were 21.4% for children from 6 months to 2 years of age and 16.1% for children from 2 to 5 years of age[12]. However, the vaccination coverage among children aged under 5 years was stable at a low level of 3-4% from 2015 to 2019 in China[13]. It is important to understand parental attitudes and preferences for vaccines and to explore key factors associated with parents' decisions to vaccinate their children.

Identifying facilitators and barriers to influenza vaccination would be important to promote

vaccination. A systematic review revealed that several facilitators for parents to accept influenza vaccination were belief in vaccine efficacy and influenza severity and susceptibility, perception of advantages of the school setting (e.g., it is very convenient to vaccinate children in school), and trust in vaccines[14]. In China, the barriers were complex. One study surveyed various populations and found that the most common reason for being unvaccinated in the influenza vaccine was worrying about the side effects[15]. Another study that targeted at quadrivalent influenza vaccine for school-aged children showed that the pivotal barriers hindering parents from having their children vaccinated were fear of side effects and no perceived susceptibility[16]. On the contrary, one study indicated that perceived severity and knowledge about influenza were not independently significantly associated with uptake[17].

Children aged 6-59 months, recommended routine influenza vaccination strongly by WHO [2], are also among the priority vaccination groups stated by the Chinese Center for Disease Control and Prevention (CDC) [10]. However, the influenza vaccine for children has not been covered by China's National Immunization Program. The decision to vaccinate against influenza for children mostly depends on parents' views and preferences. Consequently, it is crucial to understand the factors affecting parents' decisions to vaccinate their children which will help the government to implement more targeted vaccination promotion strategies, so as to improve the vaccination rate of influenza vaccine for the nation.

As a stated preference method, DCEs can simulate different hypothetical vaccination scenarios and elicit respondents' preferences. DCEs have been widely used to estimate preference for vaccines [18], such as human papillomavirus, influenza, and hypothetical vaccines [19-21]. Although there exist some DCE studies on vaccines in China, respondents normally came from one particular province [22 23]. This is the first nationwide DCE study on vaccination that aims to recruit respondents by involving

parents from ten provinces to understand the preference for influenza vaccination. This study aimed to address two research questions: i) to elicit the preference of parents when choosing influenza vaccine for their children; ii) to investigate whether there exists preference heterogeneity among respondents.

2. Methods

Discrete choice experiments are increasingly used in health economics to identify and evaluate the participants' preferences [24]. DCEs can also be used to estimate participants' willingness to pay as well as to predict program uptake rates given a set of goods or services characteristics [25 26]. In the DCE, a vaccine profile can be described by a series of attributes and their corresponding levels, and under the random utility theory, respondents choose the option with the highest utility from the alternatives presented [27]. The DCE design and analysis were conducted following the checklist and reports of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Conjoint Analysis Task Forces [28-30].

2.1 Survey design

Based on previously published literature [18 20 31], twelve attributes were identified initially. To assess the appropriateness of these potential attributes and their levels and to further narrow down the number of attributes, four experts on vaccination were interviewed face-to-face in Jinan Maternity and Childcare Hospital. Two focus groups (n=12) were also conducted. One focus group included four parents only, and the other contained one vaccine expert, three parents, and four health economics/DCE experts. They were asked to review and rank the list of attributes. Finally, five attributes were selected for this study (Table 1). The attribute levels were also decided based on the influenza vaccine instructions and clinical randomized controlled trials evidence. They have been

reviewed by experts and discussed in the focus group interviews.

[Table 1]

A D-efficient design was developed using Ngene Software (www.choice-metrics.com), which yielded 60 choice sets that were further divided into six blocks to reduce respondents' cognitive burden. To check for internal consistency, one choice set in each block was duplicated. Each respondent received one block randomly and was asked to answer 11 choice sets. For those who failed the consistency test, their data were excluded from the main analysis. Before completing DCE questions, respondents were also asked to rate the importance of five attributes.

Given vaccination is a voluntary decision, an opt-out option was included and implemented by using a two-stage response design to maximize the information gained from the respondents [32]. In the first stage, the respondents were forced to choose between two hypothetical vaccinations. Then, they were asked to confirm whether they would vaccinate their preferred option from the first stage for their children.

In addition to DCE questions (which were presented in a hardcopy questionnaire), socio-demographic characteristics of respondents and their children were collected using an iPad. A pilot was conducted among 15 parents in Beijing and Jinan in July 2019 to examine the acceptability, comprehensibility, and validity. A few modifications were implemented based on the feedback from the pilot. An example of a final choice set was shown in Figure 1.

[Figure 1]

2.2 Study population and data collection

This DCE, as well as a related DCE on parental preference on vaccination for children in general [33], were embedded in a nationwide project on Strategies of Influenza Vaccination in China study [34]. A

multistage sampling method was adopted to elicit parental values and preferences for influenza vaccines across the country, the details of which has also been reported elsewhere [33]. Initially, ten provinces/municipalities were selected according to geographical location and the level of economic development, including the eastern region (Shandong and Shanghai), western region (Gansu and Chongqing), southern region (Yunnan and Guangdong), northern region (Beijing and Jilin), middle region (Henan and Jiangxi), which can be seen in Figure 2. Next, except for three municipalities (Beijing, Shanghai, and Chongqing), in each of the other seven provinces, one provincial capital, and one non-provincial-capital city were chosen. A district and a county were randomly selected from each city. Finally, 30 parents with at least one child aged between 6 months and 5 years old were randomly recruited from each community healthcare center or station.

[Figure 2]

According to a rule of thumb suggested by Orme [35], a sample size of 75 (500*3/2*10=75) would be desirable for the main effects model based on the number of analysis cells, alternatives and choice sets. We aimed to recruit a minimum of 100 respondents in each region [26 36]. Hence, we intended to survey 60 parents in each province and 120 parents in each region.

The anonymous survey was administered between August and October 2019. Data was collected through one-by-one face-to-face interviews with parents waiting for routine vaccination for their children or remaining for observation after routine vaccination. The vaccination rates for routine vaccines, such as DTaP, HepB, were more than 95% in China [37], so the sample bias for participants recruited from the vaccination sites was very limited. Before enrolling in the survey, respondents were informed about the purpose and content of the survey by interviewers who have been trained by the research team. Electronic written consent was obtained from all respondents. The study received

ethical approval from the Peking University Institutional Review Board (IRB00001052-19076).

2.3 Statistical analysis

Responses to the hardcopy DCE questionnaire were double-entered into a database set up by the EpiData 3.1 software and then matched with other socio-demographic characteristics obtained from the iPad for statistical analyses. In cases where the number of missing DCE responses was more than two tasks or the majority of socio-demographic data was missing, respondents were excluded from the final analysis.

A mixed logit model was employed to analyze DCE data which takes into account potential preference heterogeneity [38]. The utility function can be written as below:

$$U_{ijt} = X_{ijt}\beta + \varepsilon_{ijt}$$

Where U_{ijt} is the utility that respondent i derives from choosing alternative j in the choice set t, X_{ijt} is a vector representing the levels of the attributes, β is a vector of coefficients corresponding to attribute levels, and ε_{ijt} is a random error term. The cost attribute was treated as a continuous variable, while other attributes were dummy coded. In a mixed logit model, coefficients of attribute levels are commonly assumed to follow a normal distribution to account for preference heterogeneity, i.e., β is composed of a mean coefficient as well as a standard deviation. A significant positive (negative) coefficient represents a positive (negative) preference for an attribute level. The importance of an attribute can be calculated through the difference of level coefficients in the same attribute. Therefore, the relative importance of attributes can be estimated by comparing the utility range of each attribute [39].

We further examined whether the elicited preferences varied by particular socio-demographic characteristics. Finally, vaccination update rates were predicted to facilitate the interpretation of DCE

results to decision-makers. Descriptive analyses including Student's t-test, χ^2 test, and Wilcoxon rank-sum test were adopted to compare means and proportions between subgroups, respectively. All statistical analyses were conducted using Stata 12.1 software. The mixed models were estimated by simulated maximum likelihood using the Stata command developed by Hole[40] and 2000 random draws were used to achieve stability.

2.4 Patient and public involvement

The study did not involve the patients. The public was involved at the stage of questionnaire design, pretesting, and feedback from respondents was incorporated into questionnaire revisions.

3. Results

A total of 600 parents consented and participated in the survey. Among them, 3 and 18 parents were excluded from the analysis due to missing socio-demographic information and failure in completing the majority of DCE questions, respectively. Among the remaining 579 parents, they had a mean age of 31 years old, most (79%) of them are mothers of children, and the mean age of their children was 2 years old. At the time of the survey, 355 (61%) parents were working and 337 (58%) had at least two children. Among DCE responses, 449 (78%) respondents passed the consistent test (i.e., duplicated task) and they were treated as the main study sample. There was no significant difference in socio-demographic characteristics between those who passed and who failed the consistent test except for the region (urban vs rural). More details on respondents' socio-demographic characteristics are presented in Table 2.

[Table 2]

3.1 Importance rating

Figure 3 showed the relative importance of five DCE attributes ranked by respondents prior to the pairwise choice tasks. The most important attribute was the protection rate followed by the risk of severe side effect events, whereas the out-of-pocket cost of the vaccine and duration of vaccine-induced protection were less important.

[Figure 3]

3.2 Discrete choice experiment results

The DCE results incorporating the second-stage choices and based on the main study sample are reported in Table 3. As a sensitivity analysis, the full sample analysis results are shown in Table S1 whilst the analyses on forced-choice responses from the main study sample are presented in Table S2. All attributes were statistically significant. Overall, similar patterns can be seen in the supplementary material.

Focusing on Table 3, the mixed logit model estimates suggested that the higher the protection rate, the longer the duration of vaccine-induced protection, the lower the risk of severe side effects, the lower the cost, the more likely that parents would be willing to vaccine for their children. Contrary to our initial hypothesis, respondents prefer domestic rather than imported vaccination. Most estimated standard deviations were significant, indicating the existence of preference heterogeneity among parents.

The vaccine with the lowest risk of severe side effects had the highest preference weight when compared with a relatively high risk of severe side effects, followed by the highest protection rate. And the duration of vaccine-induced protection was less important. Reducing the risk of severe side effects from high to low could yield 4.4 (2.626/0.596) times as much as utilities increasing the duration of vaccine-induced protection from 6 months to 12 months.

The coefficient of non-vaccination was significantly negative, indicating that on average the parents were more likely to vaccinate their children against influenza regardless of the vaccine profile described by attributes and levels.

[Table 3]

To evaluate whether there was a significant difference between parents with various characteristics, a series of interaction terms between respondents' characteristics and attribute levels were explored and the result was reported in Table 4. We found that parents who were beyond 30 years old or lived in urban were more likely to choose vaccination. Highly educated, those beyond 30 years old and those who lived in rural areas placed a higher weight on the highest protection rate. Those who lived in rural areas also had a stronger preference for the lowest risk of severe side effects. Other than what has been reported, we found no significant influence between attribute levels and the working status of parents and the gender of children.

[Table 4]

3.3 Predicted uptake rates for different scenarios

Figure 4 showed the results of predicted probability when changing a particular attribute level based on results reported in Table 3. Corresponding to the reference within DCE's main effect analysis, the scenario was selected as the baseline presented by 70% protection rate, 6-month duration, high risk of severe side effects, domestic and costing CNY150. For the change within an attribute, the decrease in the risk of serious adverse effects from high to low had the largest effect on preference for influenza vaccines, in which the probability of taking that vaccination increased by 86%. For the changes with multiple attributes, the vaccine with an 80% protection rate was preferred to the free one with a 12-month duration. On the other hand, the impact of cost and duration change was small. The most attractive vaccine was '⑤+⑥' one, which has the lowest risk of severe side effects and the highest

protection rate.

[Figure 4]

4. Discussion

This study has estimated parental preference for vaccinating against influenza for their children. To the best of our knowledge, this is the first nationwide study to explore parental preference for influenza vaccine delivery using DCEs in mainland China. A previous DCE study conducted in Hong Kong Special Administrative Region surveyed the adult to assess the relative effects of different factors on influenza vaccination choices [41].

We found that on average respondents from this study preferred vaccination against influenza for their children from the hypothetical vaccination scenarios, which is consistent with other DCE study findings [31 42]. The relatively high acceptance was also documented in another survey that aimed to study the knowledge, attitudes, and practices towards the influenza vaccine among young workers in China [43].

In general, all the attributes included in our study were statistically significant and preference heterogeneity existed among both observable and non-observable personal characteristics. Among all the attributes, the risk of severe side effects and the protection rate of the vaccine were the top two most important characteristics perceived by parents. Their important roles in the choice for vaccination are in line with other influenza vaccine DCE studies [20 31]. Similar findings have also been reported in other vaccines. A DCE study surveying girls' preference for HPV vaccination reported that respondents preferred low severe side effects [44] and other studies found willingness to vaccinate was closely related to vaccine safety and efficacy [42 45]. The above findings could suggest that reducing the risk of severe side effects and increasing vaccine effectiveness could be regarded as two universal

procedures to effectively achieve higher vaccination coverage.

Somewhat surprising, given the recent Changchun Changsheng vaccine incident, this study found that parents preferred the domestic vaccine to the imported vaccine. In 2017 and 2018, Changchun Changsheng Biotechnology Co., Ltd. had two consecutive cases of serious violations of the drug production quality management specification, such as fraud in the vaccine production process. It has had a very bad impact on society. However, the same finding was also reported in one recent DCE study conducted in Shanghai, even though there are substantial differences, e.g., study population [23]. One potential reason for which domestic vaccine was preferred may be that it is thought to be more effective [46] and more accessible. And the other is that the regulatory environment is more stringent. Indeed, the government facilitated a public consultation after the incident in 2018 [47], and the Standing Committee of the National People's Congress voted to adopt the first Vaccine Administration Act in 2019, which aimed to tighten vaccine regulation [48].

The out-of-pocket cost was found to be less important compared to the other attributes. Based on the calculation of uptake rates, the probability of vaccination was affected slightly by a change in cost. This differs from some previous studies in which cost was found to be an important factor driving preferences [21 39 49]. The above results were incomparable for our study due to differences in targeted vaccines. In reality, the out-of-pocket cost of the influenza vaccine is affordable when compared to the household income. For example, the highest out-of-pocket cost of the influenza vaccine made up about 1% of the monthly income in our study. Furthermore, most families in China are willing to spend more for their children [50], and the cost is not a key factor.

When studying the preference heterogeneity, the protection rate has again stood out as a key attribute that those who were older, lived in a rural area or got higher education all placed a higher

weight on a higher protection rate. By far influenza vaccine has not been included in the national immunization program schedule in China and to improve the vaccination rate in particular for people mentioned above, providing more information about as well as improving the safety and effectiveness of vaccines will be the most important factor.

Consistent with the results of our study, vaccine safety and serious adverse events are repeatedly shown to be a top concern for parents [51]. Not only the provision of information to parents or education interventions, but also communication strategies should be focused on for healthcare communicators/practitioners. Communication processes that build rapport and trust are needed. Healthcare providers play a vital part and are often the most trusted sources of vaccine information [52]. For the relevant regulatory department, the strict supervision of domestic vaccines should be strengthened to increase parents' trust in influenza vaccine, to improve the vaccination rate of influenza vaccine for children. Vaccine providers should conduct self-examination and establish good credit. On the premise of improving the safety and effectiveness of influenza vaccines, vaccine manufacturers should pay more attention to publicity and brand building.

The present study had several limitations. Firstly, our study includes 600 respondents recruited from 10 provinces (and among them, 449 of them were included for the main analysis) which maybe not large enough to represent the whole of China. However, we did not find significant regional preference heterogeneity in the analysis. Secondly, though attributes included in our study were identified and selected through previous literature, interview with experts, and focus group discussions, following the recommended procedure, we cannot guarantee that all attributes concerned with parental vaccination choice were included. Thirdly, we did not differentiate barriers and facilitators among factors associated with the vaccine, it may be more useful to distinguish between

barriers and facilitators. Finally, similar to most DCE studies, the external validity of DCE results cannot be testified. Nevertheless, the consistency test and importance rating were implemented to confirm DCE's internal validity.

5. Conclusion

Vaccinating influenza vaccines is the most effective measure to prevent the prevalence of influenza. Although WHO and the Chinese CDC have recommended the influenza vaccine to the whole population, especially the youth, the vaccination rate is extremely low. This study aimed to investigate national parents' preference for vaccinating against influenza for their children based on a nationwide sample. Based on a discrete choice experiment, the study showed that on average parents were more willing to vaccinate their children. Among the five attributes been examined, the risk of severe side effects and protection rate were key drivers of preference among parents in China, and preference heterogeneity was found among parents. The findings from this study will shed light on future policy implementation to improve the influenza vaccination rate in China.

Contributorship statement:

Conceptualization: Shunping Li, Hai Fang.

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Formal analysis: Tiantian Gong, Ping Liu.

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Methodology: Gang Chen, Tiantian Gong, Ping Liu.

Project administration: Shunping Li, Gang Chen.

Supervision: Shunping Li, Hai Fang.

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Figure titles and footnotes

Fig.1 An example of discrete choice question (translated version)

Fig.2 Provinces/municipalities selected in China

Fig.3 Importance Rating of Attributes

Fig.4 Simulated probabilities for influenza vaccination under change of a single attribute.

Notes: The baseline was presented by a 70% protection rate, 6-month duration, high risk of severe side effect, domestic and costing CNY150.

Table 1 Attributes and attributes levels for DCE choice questions

Attributes	Attributes levels		Explanation
Protection rate prevented by a vaccine	1	70%	The percentage of children that will be protected against an influenza infection when vaccinated.
	2	80%	
	3	90%	
Duration of vaccine-induced protection	1	6 months	The number of months that the vaccine protects against influenza.
	2	12 months	
The risk of serious side effects	1	1/100,000	The number of vaccinated children that will suffer from serious adverse events due to vaccination. Serious adverse events included hospitalization or prolongation of hospitalization, persistent or significant disability or incapacity.
	2	2/100,000	
	3	10/100,000	
Location of vaccine manufacturer	1	domestic	The vaccine manufacturers were divided into Chinese-made (domestic) and foreign (imported) categories
	2	imported	
The out-of-pocket cost of a vaccine	1	0 Yuan	The parents may have to pay of the vaccine cost out-of-pocket.
	2	75 Yuan	
	3	150 Yuan	

Table 2 Socio-demographic characteristics of the study population

	All (N=579)		Parents who passed the consistency test		Parents who failed the consistency test		P-value
	Mean	SD	Mean	SD	Mean	SD	
Age(years)	31.07	0.21	31.20	0.25	30.59	0.42	0.231 [a]
Household size	4.60	0.05	4.57	0.06	4.73	0.12	0.194 [a]
Monthly income(RMB)	11988.4	482.04	12025.66	480.81	11860	1365.26	0.886 [a]
Monthly expenditure(RMB)	6796.17	250.81	6894.88	274.26	6455.23	593.19	0.465 [a]
Child' age	2.00	0.05	2.02	0.06	1.93	0.11	0.462 [a]
	N	%	N	%	N	%	
Relation							
Mother	459	79.27	354	78.84	105	80.77	0.633 [b]
Father	120	20.73	95	21.16	25	19.23	
Ethnic							
Han	534	92.23	414	92.20	120	92.31	0.969 [b]
Minority	45	7.77	35	7.80	10	7.69	
Child gender							
Male	294	50.78	220	49.00	74	56.92	0.111 [b]
Female	285	49.22	229	51.00	56	43.08	
One child							
Yes	242	41.80	189	42.09	53	40.77	0.787 [b]
No	337	58.20	260	57.91	77	59.23	
Child health							
Very good	278	48.01	219	48.78	59	45.38	0.415 [c]
Good	224	38.69	173	38.53	51	39.23	
Fair or poor	77	13.3	57	12.69	20	15.38	
Job							
Working	355	61.31	278	61.92	77	59.23	0.580 [b]
Non-working	224	38.69	171	37.86	53	40.77	
Region							
Urban	357	61.66	288	64.14	69	53.08	0.022 [b]
Rural	222	38.34	161	35.86	61	46.92	
Education level							
Senior and below	211	53.71	234	52.12	77	59.23	0.152 [b]
College and above	268	46.29	215	47.88	53	40.77	

Note:

1.a-Student's test, b-χ^2 test, c-Wilcoxon rank-sum test.

Table 3. Mixed logit model results with only main effects

Attributes	β	SE	P-value	SD	SE	P-value
Non-vaccination	-5.236	0.757	<0.001	6.391	0.586	<0.001
Protection rate prevented by a vaccine (ref:70%)						
80%	0.935	0.089	<0.001	0.310	0.229	0.175
90%	1.921	0.133	<0.001	1.436	0.140	<0.001
Risk of serious side effects event (ref:10/100,000)						
2/100,000	1.795	0.116	<0.001	0.875	0.152	<0.001
1/100,000	2.626	0.158	<0.001	1.754	0.157	<0.001
Location of vaccine manufacturer (ref: domestic)						
Imported	-0.319	0.082	<0.001	1.181	0.105	<0.001
Duration of vaccine-induced protection (ref:6month)						
12 months	0.596	0.067	<0.001	0.571	0.101	<0.001
Cost	-0.002	0.001	0.016	0.011	0.001	<0.001
Log likelihood			-2648.049			
No .of respondents			449			
No. of observations			13446			

Note:

1.β-coefficient, SE-standard error, SD-standard deviation, ref-reference. All attributes except for cost were coded for dummy variables.

2. A total of 600 parents enrolled in the survey and 579 completed the majority of the questionnaire at least. Respondents (449) who passed the consistency test were included in the main DCE result reported in this table.

Table 4 Results of Mixed logit model with main effects and interactions

Attributes	β	SE	P-value	95%CI	
Non-vaccination	-6.178	0.767	<0.001	-7.680	-4.675
Protection rate prevented by a vaccine (ref:70%)					
80%	0.940	0.088	<0.001	0.767	1.113
90%	1.218	0.235	<0.001	0.758	1.679
Risk of serious side effects event (ref:10/100,000)					
2/100,000	1.804	0.116	<0.001	1.576	2.031
1/100,000	2.334	0.265	<0.001	1.815	2.854
Location of vaccine manufacturer (ref: domestic)					
Imported	-0.298	0.079	<0.001	-0.454	-0.143
Duration of vaccine-induced protection(ref:6month)					
12 months	0.583	0.065	<0.001	0.456	0.711
Cost	-0.001	0.002	0.624	-0.005	0.003
Interaction terms					
Non-vaccination * age (>30 years old)	2.843	0.778	<0.001	1.319	4.367
Non-vaccination * rural	-2.216	0.973	0.023	-4.123	-1.305
Non-vaccination * father	-0.157	0.746	0.833	-1.620	-0.302
Non-vaccination *only one child	1.017	0.967	0.293	-0.878	2.911
90% protection rate* age (>30 years old)	0.581	0.209	0.005	0.173	0.990
90% protection rate* rural	0.732	0.220	0.001	0.302	1.163
90% protection rate* education level (college and above)	0.540	0.213	0.011	0.123	0.956
90% protection rate*only one child	-0.231	0.216	0.285	-0.655	0.192
Lowest risk of serious side effects*only one child	-0.506	0.236	0.032	-0.969	-0.043
Lowest risk of serious side effects*rural	0.838	0.240	<0.001	0.367	1.309
Lowest risk of serious side effects* age (>30 years old)	0.372	0.223	0.096	-0.066	0.810
Lowest risk of serious side effects* education level (college and above)	0.291	0.230	0.206	-0.160	0.742
Log likelihood			-2631.978		
No .of respondents			449		
No .of observations			13446		

Note:

1.β-coefficient, SE-standard error, SD-standard deviation, CI-confidence interval, ref-reference. All attributes except for cost were coded for dummy variables.

2. A total of 600 parents enrolled in the survey and 579 completed the majority of the questionnaire at least. Respondents (130) who failed the consistency test were excluded from the main DCE result reported in this table.

3. Interaction terms were treated as fixed effect variables, and the others as random effect variables.

	Influenza vaccine A	Influenza vaccine B
Protection rate prevented by a vaccine	70%	90%
Duration of vaccine-induced protection	12 months	6 months
Risk of severe side effect	2/100,000	1/100,000
Location of vaccine manufacturer	domestic	imported
Out-of-pocket cost of the vaccine	0 Yuan	75 Yuan
Which option would you be more likely to choose?	☐	☐
In reality, would you vaccine your child the option you chose before	☐ Yes ☐ No	

Fig.1 An example of discrete choice question (translated version)

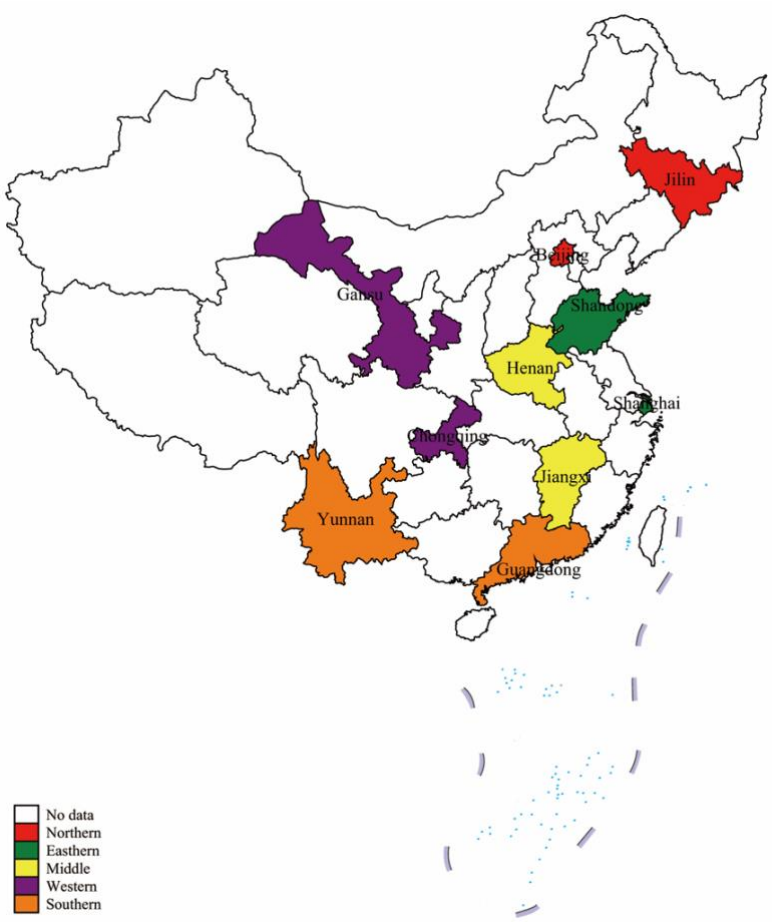

Fig.2 Provinces/municipalities selected in China

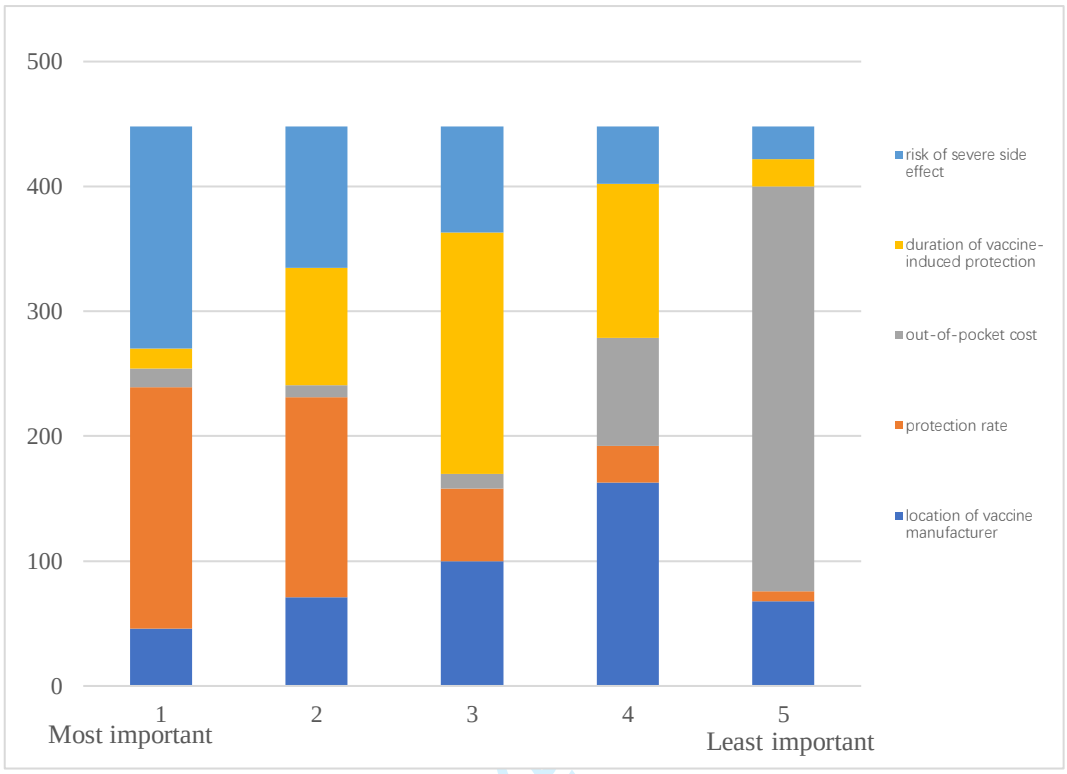

Fig.3 Importance Rating of Attributes

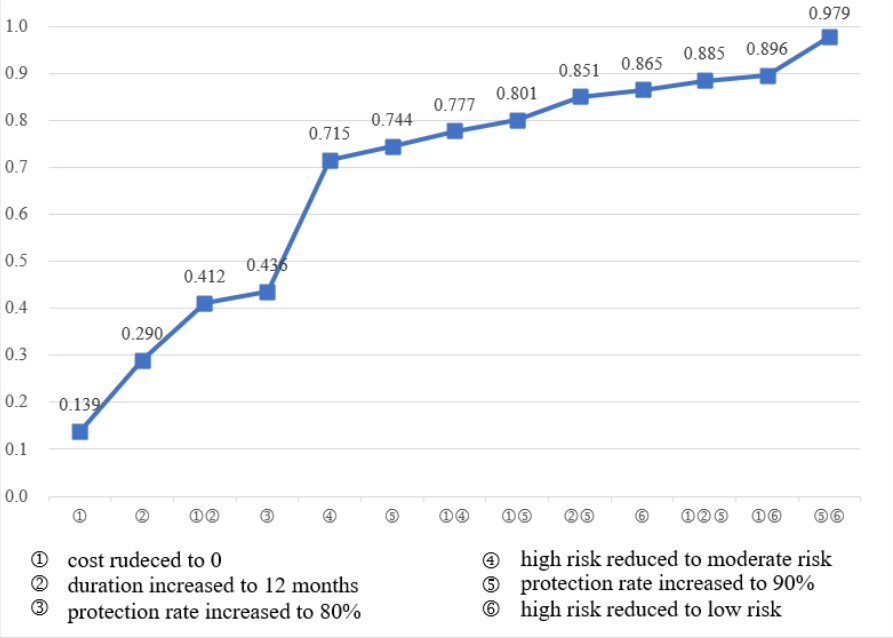

Fig.4 Simulated probabilities for influenza vaccination under change of a single attribute. The baseline was presented by a 70% protection rate, 6-month duration, high risk of severe side effect, domestic and costing CNY150.

Simulated probabilities for influenza vaccination under change of a single attribute.

SUPPLEMENTARY MATERIAL

Table S1 Mixed logit model results with only main effects for unforced choice in the full sample

Attributes	β	SE	P-value	SD	SE	P-value
Non-vaccination	-3.487	0.477	<0.001	5.172	0.455	<0.001
Protection rate prevented by a vaccine (ref:70%)						
80%	0.803	0.069	<0.001	0.065	0.303	0.830
90%	1.655	0.099	<0.001	1.187	0.104	<0.001
Risk of severe side effect event (ref:10/100,000)						
2/100,000	1.559	0.089	<0.001	0.794	0.126	<0.001
1/100,000	2.205	0.116	<0.001	1.539	0.124	<0.001
Location of vaccine manufacturer (ref: domestic)						
Imported	-0.257	0.062	<0.001	0.934	0.080	<0.001
Duration of vaccine-induced protection (ref:6month)						
12 months	0.594	0.055	<0.001	0.599	0.090	<0.001
Cost	-0.002	0.001	0.010	0.010	0.001	<0.001
Log likelihood			-3709.407			
Respondents, n			579			
Observations, n			17337			

Note:

1.unforced choice-parents can choose to not vaccinate influenza vaccines for their children and the opt-out choice in the second stage was analyzed in the model.

2.β-coefficient, SE-standard error, SD-standard deviation, ref-reference. All attributes except for cost were coded dummy variables.

3. A total of 600 parents enrolled in the survey and 579 completed the majority of the questionnaire.

Table S2 Mixed logit model results with only main effects for forced-choice data

Attributes	β	SE	P-value	SD	SE	P-value
Protection rate prevented by a vaccine (ref:70%)						
80%	0.794	0.078	<0.001	0.104	0.354	0.769
90%	1.679	0.119	<0.001	1.271	0.128	<0.001
Risk of severe side effect event (ref:10/100,000)						
2/100,000	1.718	0.111	<0.001	0.982	0.141	<0.001
1/100,000	2.558	0.156	<0.001	1.774	0.154	<0.001
Location of vaccine manufacturer (ref: domestic)						
Imported	-0.248	0.072	0.001	1.050	0.093	<0.001
Duration of vaccine-induced protection (ref:6month)						
12 months	0.526	0.060	<0.001	0.520	0.098	<0.001
Cost	-0.001	0.001	0.190	0.010	0.001	<0.001
Log likelihood			-2399.908			
Respondents, n			477			
Observations, n			9538			

Note:

1.forced choice: parents were forced to choose the preferred vaccine from alternatives presented and the choice in the first stage was analyzed in the model.

2.β-coefficient, SE-standard error, SD-standard deviation, ref-reference. All attributes except for cost were coded dummy variables.

3. A total of 600 parents enrolled in the survey and 579 completed the majority of the questionnaire at least. Respondents (477) who passed the consistency test in the first stage were included in the main effects DCE result reported in this table.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*NA*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
Outcome data	15*	Report numbers of outcome events or summary measures	11,12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA

		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11,12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13,14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.