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Cost-effectiveness analysis of influenza vaccination during pregnancy in Japan

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ABSTRACT

Background: Pregnant women and infants are known as high risk groups for influenza. WHO recommend pregnant women be vaccinated with inactivated influenza vaccine. In Japan, some municipalities started to give subsidy to encourage pregnant women to receive a shot on their own accord, which has made the introduction of seasonal antepartum maternal vaccination program (AMVP) into the routine vaccination list a current topic in health policy and has raised the need to evaluate the value for money of such possibility.

Methods: We conducted a cost-effectiveness analysis to evaluate the efficiency of conducting AMVP in Japan. A decision tree model was adopted taking into consideration the duration of single-year vaccine effectiveness for infants and for mothers. The program targeted pregnant women aged 20–49 years old at or over 12 weeks gestation during October 1 through March 30. Estimated probabilities of treatments received due to influenza for pregnant/postpartum women or their infants varied by calendar time, vaccination status, and/or gestational age. Incremental cost-effectiveness ratio (ICER) compared with current no-AMVP from societal perspective was calculated. Transition probabilities, utility weights to estimate quality-adjusted life year (QALY), and disease treatment costs were either calculated or extracted from literature. Costs per vaccination was assumed at ¥3,529/US$32.1.

Results: AMVP reduces disease treatment costs, while the reduction cannot offset the vaccination cost. Incremental QALYs were at 0.00009, among them 84.2% were from infants. ICER was ¥7,779,356/US$70,721 per QALY gained. One-way sensitivity analyses revealed that vaccine effectiveness for infant and costs per shot were the two main key variables affecting the ICER.

Conclusion: We found that vaccinating pregnant women with influenza vaccine to prevent unvaccinated infants and pregnant/postpartum women from influenza-associated disease in Japan can be cost-effective from societal perspective, under the WHO-suggested "cost-effective" criteria (1–3 times of GDP).

1. Introduction

Pregnant women have increased risk of severe disease and death from influenza with the infection leading to possible complications such as stillbirth, neonatal death, preterm delivery, and decreased birth weight [1]. Infants aged <6 months are particularly at high risk for influenza-associated hospitalization, since their immune response to inactive influenza vaccination is relatively poor [2,3]. The risk groups for influenza, as defined by World Health Organization (WHO), include pregnant women, children aged <5 years old, the elderly, and individuals with underlying health conditions such as HIV. According to WHO, "countries considering the initiation or expansion of programs for seasonal influenza vaccination, pregnant women should have the highest priority. Whereas, countries with existing influenza vaccination programs targeting children aged 6–59 months, the elderly, individuals with specific chronic medical conditions, or health-care workers, should incorporate immunization of pregnant women" [4]. WHO recommended that "the pregnant women be vaccinated with trivalent inactivated influenza vaccine (TIV) at any stage of pregnancy, based on the evidence that TIV is safe throughout

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pregnancy and it is effective in preventing influenza in women as well as their infants" [4]. Vaccination programs targeting pregnant women were shown to be cost-effective from England and Wales, Belgium, and Canada [5–7], whereas vaccination of pregnant women with additional co-morbidities was found to be cost-saving from the United States [8].

In Japan, only people aged 65 or over and people aged 60–64 with underlying conditions are eligible for routine vaccination based on the Immunization Act. While during the 2009 H1N1 pandemic, Ministry of Health, Labour and Welfare (MHLW) announced that pregnant women were included in the priority list to receive H1N1pdm09 vaccine, wherein more than 60% of pregnant women were vaccinated within 1.5 months after the vaccine's availability [9,10]. Seasonal TIV had been substituted by quadrivalent inactivated influenza vaccine (QIV, an egg-derived vaccine produced by four domestic pharmaceutical companies) from 2015/16 season. While influenza vaccination on pregnant women is not on the routine vaccination list, pregnant women can avail the vaccine at personal expense. Amidst the lack of a national/regional vaccine coverage, previous cohort studies on vaccine effect/disease burden indicated vaccine uptake rates ranging from 20 to 50% [11–15]. Recently, some municipalities started to give subsidy to encourage pregnant women to receive a shot on their own accord, which has made the introduction of seasonal maternal influenza vaccination into the routine vaccination list a current topic in health policy and has raised the need to know whether the benefit of vaccination justify its added costs. Our study aimed to estimate the value for money of vaccinating pregnant women by using QIV in Japan, assuming that in the future, Japan may need to consider the implementation of this strategy.

2. Method

2.1. Literature search

We searched various databases for the parameters, which were included in the modeling. Studies pertaining to epidemiology and prognosis of influenza-relevant disease in Japan's setting were accessed from Medline database, Igaku Chuo Zasshi database (a Japanese medical bibliographic database which contains over 10 million citations originating from Japan), MHLW Grant System, and annual statistical reports published by the government. Due to insufficient evidences from Japan, overseas' reports from Medline, The Cochrane Database of Systematic Reviews, Health Technology Assessment database, and National Health Service, Economic Evaluation Database regarding vaccine effectiveness and utility weights to estimate QALY were used instead.

2.2. Models and variables

A decision tree model was used to estimate the cost-effectiveness of 1-dose antepartum maternal seasonal influenza vaccination program (AMVP) by comparing with current no-AMVP strategy. AMVP targeted pregnant women aged 20–49 years old at or over 12 weeks gestation, during one influenza season. Though WHO recommended that a vaccine can be received at any stage of pregnancy, in our model, we assumed that they will receive the vaccine at a gestational age of ≥12 weeks (i.e, from second to third trimester). The choice of gestational age is supported by the frequency of use of inactive influenza vaccine, which supports vaccine safety during pregnancy [16], compared the less frequent use of the recently licensed QIV [17]. The benefits of vaccination included the prevention of influenza in pregnant women/postpartum mothers and their infants (aged <6 months). Effectiveness of the strategy was estimated in quality-adjusted life years (QALYs) to account for both time and quality of life of prevented influenza cases. The incremental cost-effectiveness ratio (ICER) was estimated by dividing the difference in net cost in AMVP and no-AMVP strategy by the difference in QALY gained between the two strategies.

We estimated ICER from societal perspective, which in this case is also payer's (including government, municipalities, vaccinees, patients, and third-party payers) perspective, because pregnant women tend to uptake a shot in their routine prenatal visit, and maternity leave (six weeks ahead of expected date of birth to eight weeks after delivery for all the female employees) as well as child-care leave (one year for male/female employee) are provided under Japanese law. Therefore, there is no need to consider productivity loss due to vaccination or disease treatment.

Our model assumed: (1) even in the last month of pregnancy, women will uptake the vaccine if they are willing to do so, (2) if a pregnant women has a gestational age of <12 weeks by the end of calendar months from October to January, catchup vaccination will be done from November to March when her gestation age reaches ≥12 weeks, (3) a 4-week delay before vaccinees benefit from vaccine protection [18–20], (4) vaccination given 1 month before delivery confers seroprotection to neonates, though study reported 2 weeks [21], (5) no association between maternal influenza vaccination and adverse birth outcomes [22], (6) influenza season is from October through April, (7) vaccine supply would be available on Oct 1, and is assumed to be sufficient throughout the season, (8) vaccine effectiveness (VE) is not expected to last until the next flu season, and (9) all pregnancies are singleton to simplify the model (multiple pregnancy is low in Japan at 1.04% in 2017) [23].

In the decision tree (Fig. 1), the targeted pregnant women were assumed to firstly decide whether or not and when (any month from October to March) to receive a flu shot. Regardless of vaccination status, the model then continued with livebirth or stillbirth. In the mother with livebirth branch, the costs of treatment (if any) as well as QALYs of the mother and her infant will be combined. On the other hand, in the mother with stillbirth branch, only costs and QALYs of mother were included. Pregnant /postpartum women (regardless of vaccination status) and infants (regardless of his/her mother's vaccination status) followed by any of the following three or four outcomes, respectively: (1) not had influenza, (2) received outpatient treatment due to influenza and recovered from illness, (3) hospitalized due to influenza and recovered from illness, and (4) deaths related to seasonal influenza (infant only). No maternal deaths occurred with regard to seasonal influenza based on a report in 2009 [9]. The no-vaccination branch was identical with the vaccination branch except that VE will apply only on vaccination branch. Adverse effects of vaccination were not incorporated based on reports from the study of Jackson et al. [24]. Herd immunity was not considered because pregnant women were only a part of the population and not a key population related to transmission [25]. The model was built using TreeAge Pro software (version 2019; TreeAge, Inc, Williamstown, MA).

2.3. Parameters in model

Probability that a pregnant woman received a shot in current no-AMVP strategy, at 0.27, was from Ohfuji et al. [14]. On the other hand, the probability for AMVP strategy, at 0.60, was based on the H1N1 monovalent vaccine coverage rate and vaccine uptake rates reported by cohort studies on seasonal influenza disease burden [9–15].

The percentage of receiving a shot by month (from October to March), 14.8%, 35.2%, 48.0%, 0.67%, 0.67%, and 0.67%, respectively, were based on the estimation of cumulative supply of QIV by month in 2018/19 season [26]. Month-specific probability of a

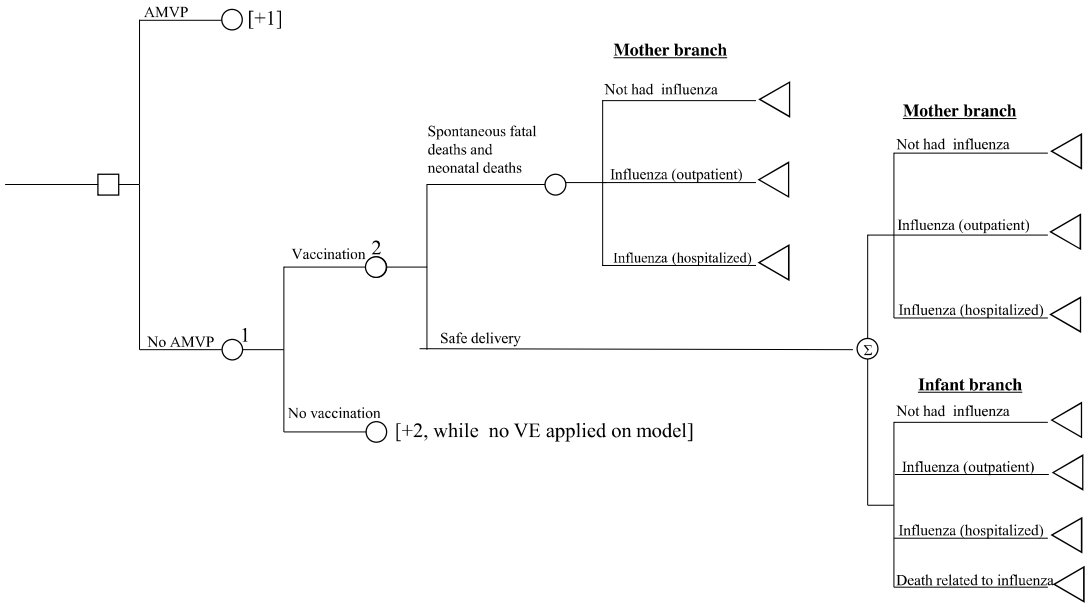

Fig. 1. Decision tree model. □: Decision node; ○: Chance node; Σ: Sum of both mother's and infant's results. AMVP: antepartum maternal seasonal influenza vaccination program. VE: vaccine effectiveness.

target delivery and a stillbirth occurrence, were based on Vital Statistics and perinatal mortality in Japan [23]. Since we aimed to estimate the difference of costs and QALYs between two strategies, probabilities of a pregnant woman receiving outpatient treatment due to influenza were conditional on the timing of a woman who received vaccine and the length of expected VE. For instance, if vaccine was received in October, the expected VE length is from November to April, with the probability estimated as "cumulative number of influenza patients from November to April/corresponding population". Expected VE length is assumed to start from the month after the shot was received until April the succeeding year, for example if received in November, expected VE length is from December to April and, if December, then January to April. Expected VE length, however, will only be in April if the shot was received in March. For infants, the probability of receiving outpatient treatment due to influenza was conditional on maternal vaccination status and birth month by calendar. For example, if born in November, the probability was estimated as "cumulative number of influenza patients from November to April/corresponding population"; if born in December, from December to April and if born in April, "April only", etc. While if born in May or after, there is no need to estimate the probability since it is beyond the influenza season in Japan. Population and cumulative number of influenza patients were from Vital Statistics [27] and "number of influenza patients from weekly surveillance report for the 2018/19 season" published by the National Institute of Infectious Diseases (NIID) [28], respectively. Since there are no direct data which reported the influenza incidence or number of influenza patients of pregnant women and infants aged under 6 months, we instead used the data of 20–49 years old for pregnant/postpartum women and 0–4 years old for infants, to estimate these probabilities. Fig. 2 shows the weekly reports of numbers of influenza patients (0–4 years old and 20–49 years old) by NIID. Cases in NIID reports [28] may not be laboratory-confirmed influenza, but physician-diagnosed influenza. In Japan, influenza rapid diagnostic test is routinely performed for patients who visit clinics and hospital for treatment of acute febrile respiratory illnesses during the influenza season [14]; we considered using this information to estimate the probability whenever appropriate. The probabilities of being hospitalized among outpatient influenza patients for pregnant/postpartum women, 0.023, was from Yamada et al. [11], while for infant patients, it was assumed at 0.20 based on Ohfuji et al. [14]. Probability that any infant dies of influenza (0.28 per 100,000) was based on 2009 H1N1 epidemic [29]. All these data were shown in Table 1.

2.4. Vaccine effectiveness

VE in reducing illness due to influenza for infants born to vaccinated mothers was assumed at 61% (95% confidence interval (CI): 15–81%) based on a cohort study by Ohfuji et al. [14], which is the first study that reported the effects of maternal vaccination (prenatal and postpartum) on influenza among infants by using a large cohort of infants (n > 3,000). VE for infants was assumed to last the entire 6 months after delivery [14,19]. The study period of Ohfuji et al. spanned throughout the whole influenza season, which means, the waning immunity of vaccine, as pointed by some studies [30,31], was already included in the reported VE. Thus, the use of the 61% in base-case and 95% CI in sensitivity analysis are fully justified. Few studies evaluated VE against seasonal influenza for pregnant women and since the results are inconsistent [20,32–34], we assumed 50% as VE for pregnant women/postpartum women, based on (1) Cochrane review reported for pregnant women is at 50% for pH1N1-containing vaccine [35], and (2) the pooled VE (14.5–71.2%) for healthy adults from eight studies [36].

2.5. Utilities

The utility weights for pregnant/postpartum women who received outpatient treatment were based on a study by O'Brien et al. [37]. O'Brien et al. reported the health state utility scores (measured by visual analog scale) from adult patients with influenza infection who received oseltamivir treatment from day 1 to day 7 (the scores are 0.42, 0.50, 0.61, 0.69, 0.75, 0.79, and 0.82, respectively). Assuming that the duration of influenza was 7 days, QALY was estimated as (0.42 + 0.50 + 0.61 + 0.69 + 0.75 + 0.79 + 0.

Table 1
Variables.

Number and percentage of birth and fetal death by month					[23]
	Birth (%)	Fetal death (%)			
Jan	75,528 (8.63)	772 (1.01)			
Feb	71,898 (8.22)	873 (1.20)			
Mar	78,471 (8.97)	843 (1.06)			
Apr	75,255 (8.60)	755 (0.99)			
May	80,890 (9.24)	786 (0.96)			
Jun	77,035 (8.80)	822 (1.06)			
Jul	84,390 (9.64)	766 (0.90)			
Aug	85,456 (9.77)	852 (0.99)			
Sep	84,899 (9.70)	818 (0.95)			
Oct	–	–			
Nov	78,239 (8.94)	829 (1.05)			
Dec	83,027 (9.49)	767 (0.92)			
Estimated probabilities of receiving outpatient treatment due to influenza by delivery due date (conditioned on length of vaccine effectiveness; VE)					[27,28]
	Pregnant/postpartum women		Infants		
	Lengths of VE	Estimated probabilities of receiving outpatient treatment	Lengths of VE	Estimated probabilities of receiving outpatient treatment	
Due date 4/15 (12-week gestation date: 10/12)					
vaccinated in Oct	Nov-Apr	0.0131	Apr	0.0095	
vaccinated in Nov	Dec-Apr	0.0156			
vaccinated in Dec	Jan-Apr	0.0180			
vaccinated in Jan	Feb-Apr	0.0090			
vaccinated in Feb	Mar-Apr	0.0024			
vaccinated in Mar	Apr	0.0023			
Due date 3/15 (12-week gestation date: 9/1)					
vaccinated in Oct	Nov-Apr	0.0131	Mar-Apr	0.0108	
vaccinated in Nov	Dec-Apr	0.0156			
vaccinated in Dec	Jan-Apr	0.0180			
vaccinated in Jan	Feb-Apr	0.0090			
vaccinated in Feb	Mar-Apr	0.0024			
vaccinated in Mar	Apr	0.0023	–	–	
Due date 2/15 (12-week gestation date: 8/3)					
vaccinated in Oct	Nov-Apr	0.0131	Feb-Apr	0.0459	
vaccinated in Nov	Dec-Apr	0.0156			
vaccinated in Dec	Jan-Apr	0.0180			
vaccinated in Jan	Feb-Apr	0.0090			
vaccinated in Feb	Mar-Apr	0.0024	–	–	
vaccinated in Mar	–	–	–	–	
Due date 1/15 (12-week gestation date: 7/3)					
vaccinated in Oct	Nov-Apr	0.0131	Jan-Apr	0.1095	
vaccinated in Nov	Dec-Apr	0.0156			
vaccinated in Dec	Jan-Apr	0.0180			
vaccinated in Jan	Feb-Apr	0.0090	–	–	
vaccinated in Feb	–	–	–	–	
vaccinated in Mar	–	–	–	–	
Due date 12/15 (12-week gestation date: 6/2)					
vaccinated in Oct	Nov-Apr	0.0131	Dec-Apr	0.0913	
vaccinated in Nov	Dec-Apr	0.0156			
vaccinated in Dec	Jan-Apr	0.0180	–	–	
vaccinated in Jan	–	–	–	–	
vaccinated in Feb	–	–	–	–	
vaccinated in Mar	–	–	–	–	
Due date 11/15 (12-week gestation date: 5/3)					
vaccinated in Oct	Nov-Apr	0.0131	–	–	
vaccinated in Nov	Dec-Apr	0.0156	–	–	
vaccinated in Dec	–	–	–	–	
vaccinated in Jan	–	–	–	–	
vaccinated in Feb	–	–	–	–	
vaccinated in Mar	–	–	–	–	
Due date 9/15 (12-week gestation date: 3/3)					
vaccinated in Oct	–	–	–	–	
vaccinated in Nov	–	–	–	–	
vaccinated in Dec	–	–	–	–	
vaccinated in Jan	–	–	–	–	
vaccinated in Feb	–	–	–	–	
vaccinated in Mar	Apr	0.0023	–	–	

Table 1 (*continued*)

Number and percentage of birth and fetal death by month					[23]
	Birth (%)	Fetal death (%)			
Due date 8/15 (12 week gestation date: 1/31)					
vaccinated in Oct	–	–	–	–	
vaccinated in Nov	–	–	–	–	
vaccinated in Dec	–	–	–	–	
vaccinated in Jan	–	–	–	–	
vaccinated in Feb	Mar-Apr	0.0024	–	–	
vaccinated in Mar	Apr	0.0023	–	–	
Due date 7/15 (12-week gestation date: 12/31)					
vaccinated in Oct	–	–	–	–	
vaccinated in Nov	–	–	–	–	
vaccinated in Dec	–	–	–	–	
vaccinated in Jan	Feb-Apr	0.0090	–	–	
vaccinated in Feb	Mar-Apr	0.0024	–	–	
vaccinated in Mar	Apr	0.0023	–	–	
Due date 6/15 (12 week gestation date: 12/2)					
vaccinated in Oct	–	–	–	–	
vaccinated in Nov	–	–	–	–	
vaccinated in Dec	Jan-Apr	0.0180	–	–	
vaccinated in Jan	Feb-Apr	0.0090	–	–	
vaccinated in Feb	Mar-Apr	0.0024	–	–	
vaccinated in Mar	Apr	0.0023	–	–	
Due date 5/15 (12-week gestation date: 10/31)					
vaccinated in Oct	–	–	–	–	
vaccinated in Nov	Dec-Apr	0.0156	–	–	
vaccinated in Dec	Jan-Apr	0.0180	–	–	
vaccinated in Jan	Feb-Apr	0.0090	–	–	
vaccinated in Feb	Mar-Apr	0.0024	–	–	
vaccinated in Mar	Apr	0.0023	–	–	
Estimated probability of being hospitalised among outpatient patient					
Pregnant/postpartum women)				2.3%	[11]
Infants				20.0%	[14]
Probability of an infant dies of influenza				0.28 per 100,000	[29]
Life expectancy of surviving infant (3% discount); years				34.42	[44]
Vaccine effectiveness (VE)					
Infants				61%	[14]
Pregnant/postpartum women				50%	[35,36]
Utility weights					[37–41]
No influenza	1				
Outpatient	Pregnant/post-partum woman: 0.9934; infant:0.9930				
Hospitalization	Pregnant/post-partum woman: 0.9892; infant:0.9880				
Death	0				
Costs per vaccination		¥3,529			[42]
Costs for outpatient treatment/case		Pregnant/post-partum woman: ¥15,000			[43]
		Infant: ¥10,000			Estimated
Costs for hospitalization Treatment/case		Pregnant/post-partum woman: ¥609,186			[38]
		Infant: ¥286,339			[38]

82 + 365–7)/365 = 0.9934. For hospitalized patients, we assumed that the worst utility, 0.42, continued for 3 days then was similar to outpatients' (0.82) at day 9, which also continued for 3 days, based on a study which reported that 11 days was the average length of hospital stay of Japanese patients with influenza [38]. Thus, the QALY was estimated as 0.42 × 3 + 0.50 + 0.61 + 0.69 + 0.75 + 0.79 + 0.82 × 3 + 365–11)/365 = 0.9892. Since the literature search did not identify any study reporting the utility related to influenza disease of infants < 6 months, we utilized 0.9930 and 0.9880 for outpatient and hospitalized patient, respectively, from previous cost-effectiveness studies [39–41]. We assumed there were no differences between infants born to vaccinated mothers or unvaccinated mothers similar to previous studies.

2.6. Costs

The amount of direct payments to health care providers by government, municipalities, vaccinees, patients, and third-party payers was estimated as cost, while non-direct medical costs related to AMVP were not included, because we assumed that AMVP will be built within the public health services routine. Vaccination cost per shot (included doctor's fee for medical advice and technical fee for administering), ¥3,529/US$32.1 (1US$ = ¥110), was the national average costs per shot for adult without any public subsidy in 2018/19 season [42]. Treatment cost per case for hospitalized pregnant/postpartum women and infants, ¥609,186/US$5,538 and ¥277,480/US$2,523, respectively, were from Srumasiri et al. [38], which used administrative database (including approximately 4,400,000 patients, representing approximately 3% of the total Japanese population) to report the mean total healthcare cost of hospitalized influenza patients. Treatment costs per case for outpatient pregnant/postpartum women, at ¥15,000/US$136, was from Kaji et al. [43], for infants, at ¥10,000/US$91 was estimated by using national fee schedule. For infants who died due to influenza, we assumed a 2-day stay in neonatal intensive care unit (NICU) amounting to costs assumed at ¥486,339/US$4,421 (costs of hospitalization plus associated costs in NICU).

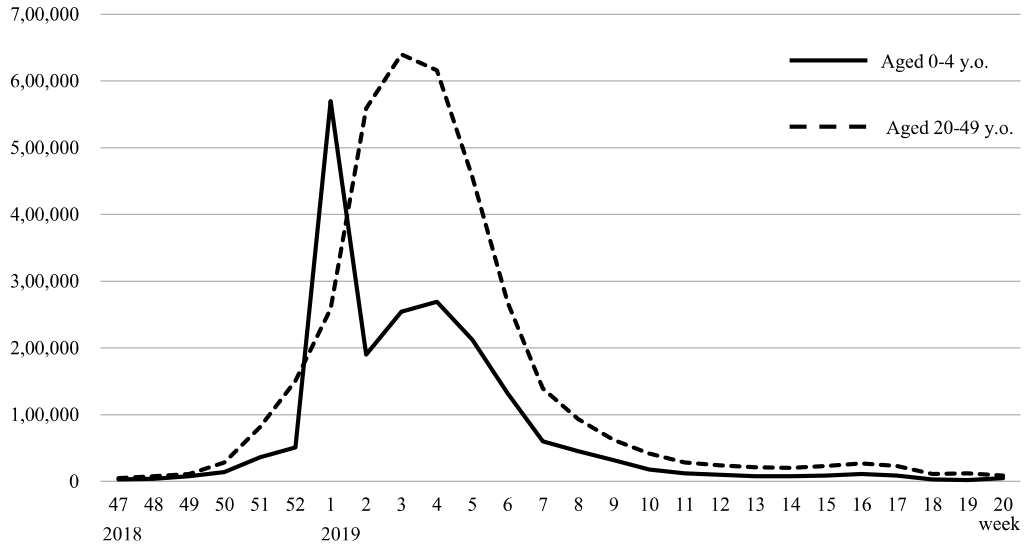

Fig. 2. Estimated number of patients who visited medical institutions nationwide by week during 2018/19 influenza season from 'Numbers of influenza patients weekly surveillance report for the 2018/19 season' reported by National Institute of Infectious Diseases.

3. Discounting

Costs related to influenza occurred in single season, therefore no discount rate was applied. Life expectancy, 34.2 years [44] for an infant who survived, was discounted at an annual rate of 3% [45].

4. Sensitivity analyses

To appraise the ICERs' stability with the assumptions made in our economic model, we performed one-way sensitivity analyses with variables and the uncertainties utilized in the model. Probabilistic sensitivity analyses (PSA) [45], i.e., 1000 Monte Carlo simulations, were also conducted. We used a triangular distribution for costs, VEs, utility weights, and a uniform distribution for probabilities.

5. Cost-effectiveness threshold

Since there is no established threshold in judging the cost-effectiveness of public health programs in Japan, a willingness-to-pay threshold at ¥5,000,000 (US$45,455) per QALY gained was utilized; a suggested threshold for evaluating healthcare interventions [46]. Also, WHO suggests a "cost-effective" criterion at 1–3 times of GDP [47]. These criteria were used in determining whether the immunization program was cost-effective or not.

6. Results

Table 2 shows the results of base-case analyses. Compared with current no-AMVP strategy, we estimated an average incremental effectiveness of AMVP at 0.00009 QALYs, among them 84.2% were from infant, the remaining 15.8% were from pregnant/postpartum woman. Though AMVP reduces disease treatment costs, the reduction cannot offset the vaccination costs. Estimated ICER was at ¥7,779,356 (US$70,721)/QALY gained.

Fig. 3 shows the impact of individual parameters to ICER. Two variables which changed the ICER to be greater than ¥1,000,000 (US$9,091)/QALY were vaccine cost and VE against infant from outpatient treatment due to influenza.

Fig. 4 shows the cost-effectiveness acceptability curve (CEAC) of AMVP compared to current no-AMVP. Among 1,000 ICERs produced by Monte Carlo simulations, the probabilities that ICER is under ¥5,000,000 (US$45,455) and ¥10,000,000 (US$90,909) per QALY gained was at 12.1% and 70.2%, respectively. Mean ICER was ¥8,397,429/ US$76,340 (SD = ¥3,511,310/US$31,921) per QALY.

7. Discussion

We conducted the first cost-effectiveness analysis in Japan comparing AMVP (using QIV) to current no-AMVP strategy. Results showed that ICER of AMVP, ¥7,779,356/US$70,721 was under the WHO-suggested "cost-effective" criterion at 1–3 times of GDP

Table 2
Results.

Strategy	Vaccination cost (¥)	Disease treatment cost (¥)		Total cost (¥)	Effectiveness (QALY)		Total Effectiveness (QALY)	ICER
		mother	infant		mother	infant	both	Base-case
No-AMVP	953	318	1,644	2,915	0.999925	35.06013	36.06006	–
AMVP	2,117	258	1,248	3,623	0.999939	35.06021	36.06015	7,779,356

AMVP: Antepartum maternal vaccination program.
QALY: Quality adjusted life year.
ICER: Incremental cost-effectiveness ratio.

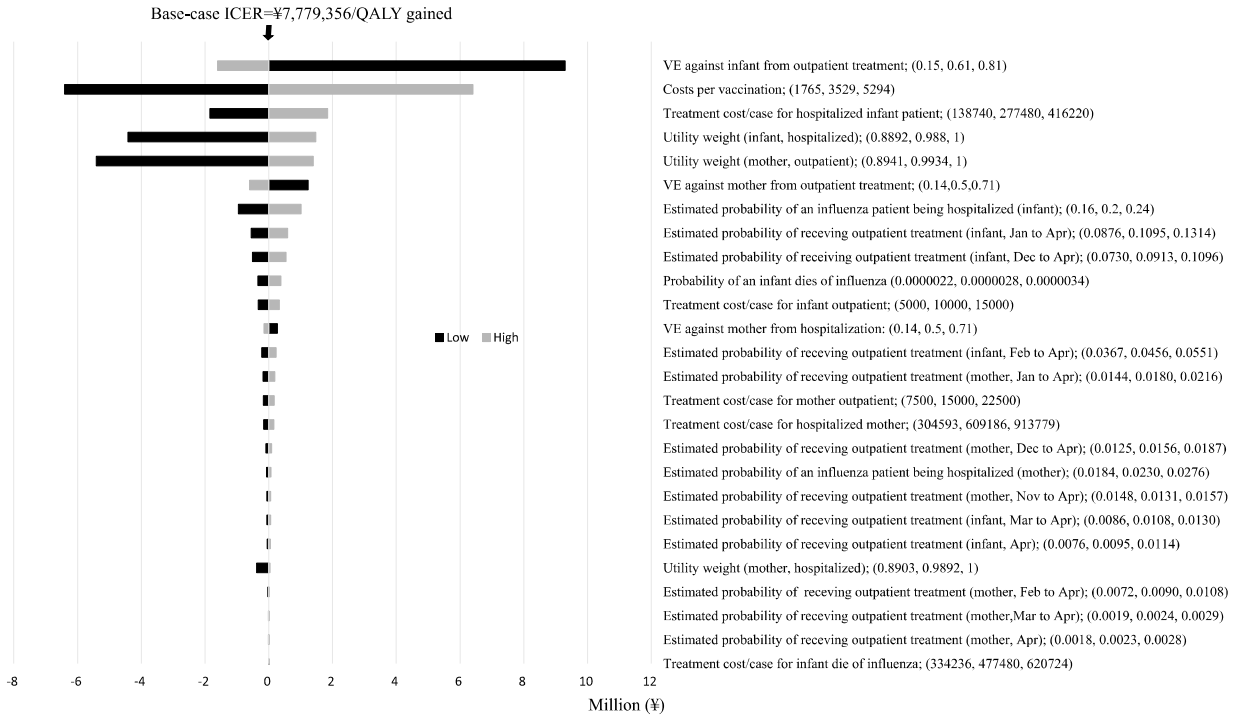

Fig. 3. Tornado diagrams (a consolidated set of one-way sensitivity analyses). Two variables which changed the ICER to be greater than ¥1,000,000 (US$9091)/QALY were VE against infant from outpatient treatment and vaccination costs.

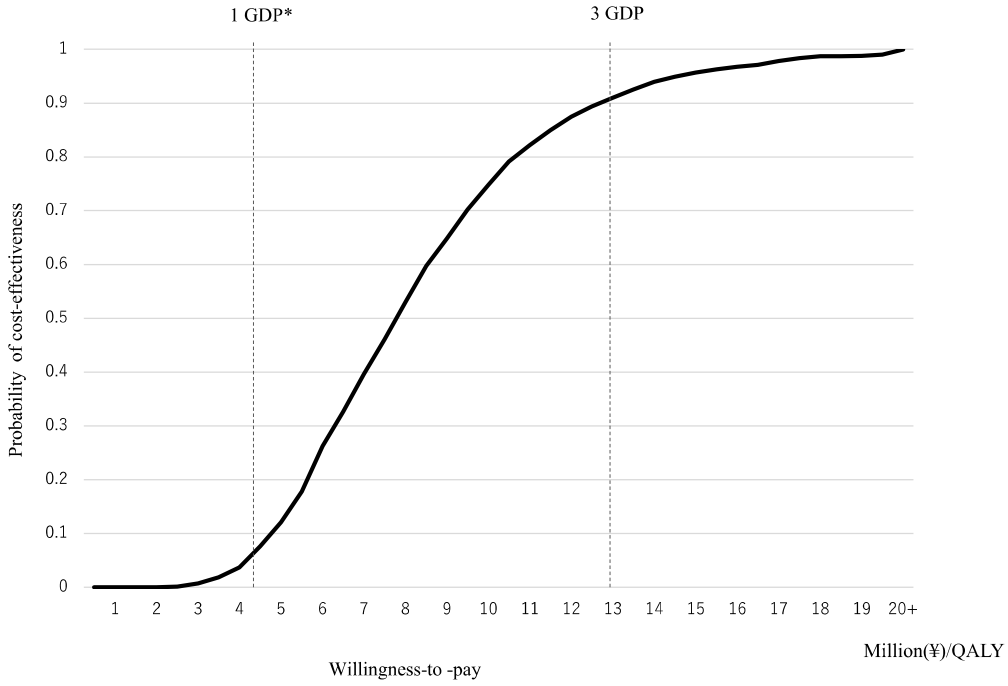

Fig. 4. Results of probabilistic sensitivity analysis: cost-effectiveness acceptability curve (CEAC). Among 1,000 ICERs generated by Monte Carlo simulation, the probabilities that ICER is under ¥5,000,000 (US$45,455) /¥10,000,000 (US$90,909) per QALY gained was at 12.1%/70.2%. For costs, VE, and utility weights, triangular distributions were used, whereas for probabilities, uniform distributions were used. The lower and upper limit of each variable is shown on Fig. 3. *¥4,419,633/US$40,263 year 2019.

(¥11,000,000/US$100,000 in Japan) [47]. One-way sensitivity analyses showed that "VE protect infant from outpatient treatment" and "costs per shot" were the two key variables which have large impacts on the results. PSA showed that the probabilities of AMVP to be under ¥5,000,000 (US$45,455) and ¥10,000,000 (US$90,909) per QALY are 12.1% and 70.2%, respectively. Mean ICER ¥8,397,429/

US$76,340 derived from PSA was favored than that of deterministic analysis mainly due to the usage of high upper limit of utility weight of influenza related disease, which led to less QALY gained and eventually contributed to higher ICER.

Since our study is the first study which evaluated the value for money of AMVP in Japan, no comparison can be done within same healthcare setting. Nevertheless, the current study is be comparable to a study which evaluated the cost-effectiveness of using pertussis-containing vaccine among pregnant women (AMVP-pertussis) in Japan [48] as well as studies from overseas. The model of AMVP-pertussis was similar to the current study, wherein the vaccine coverage rate of AMVP-pertussis was based on influenza vaccine coverage among pregnant women in Japan in 2009 H1N1 pandemic. The estimated incidence rate of 0.0140 from the AMVP-pertussis study was similar to the estimated incidence from November to April (0.0131) or from December to April (0.0156), while was slightly lower than the incidence from January to April (0.180), and was relatively higher than the incidence from February/ March/April to April (0.0090/0.0024/0.0023) in our study. The estimated ICER of AMVP-pertussis was higher than that of our study (¥9,149,317/US$93,176 vs. ¥7,779,356/US$70,721 per QALY). Higher vaccination costs per shot of pertussis-containing vaccine than that of influenza vaccine (¥6,000/US$54.5 vs. ¥3,529/US$32.1) was considered as one of the main reasons which can contribute to higher ICER. The authors used the same 'cost-effective' criteria similar to our study (1–3 times of GDP, suggested by WHO) to conclude the cost-effectiveness of AMVP-pertussis in Japan. We found seven studies which evaluated cost-effectiveness of TIV maternal immunization programs from high-income countries [5–8,39–41]. Among them, three studies, which utilized the payers' perspective, concluded that AMVP against influenza was cost-effective [5,6,8]. The other four studies, which were from a societal perspective were all from USA [7,40,41]. Roberts et al. reported that AMVP is cost-saving without the inclusion of the benefit in protecting infants [7]. Similarly, Myers et al. and Beigi et al. reported cost-effective [40,41]. Xu et al. (2016) also reported the cost-effectiveness in moderate or severe influenza seasons, but not in mild influenza seasons [39]. Among these four studies, the incidence rates of the former three studies were based on incidence rates reported in the pre-pandemic period or even cited from the study of other country, while the last one derived the rates from CDC surveillance data (weekly information), which the authors highlighted as an advantage of their study. The rates (probabilities) in our study, though were conditioned on period that VE can be expected, were estimated by using data from 'Number of influenza patients from weekly surveillance report for the 2018/19 season' published by NIID (weekly reports), which can also be an advantage in the current study. Among the seven previous studies, five added discounted life expectancy to pregnant/-postpartum women and infants who survived from influenza season [6,39–41]. Whereas in our model, no maternal mortality was assumed based on the data of 2009 H1N1 pandemic. Due to the 2009 H1N1 pandemic, Japanese physicians and pregnant women have paid more attention to the seasonal influenza [9]. In 2009 pandemic, more than 60% of pregnant women were vaccinated within 1.5 months after the availability of a vaccine. The active use of antiviral drugs for prophylaxis after close contact with an infected person and an immediate use of antiviral drug (of approximately 90% hospitalized pregnant patients) within 48 h after symptom onset [9], contributed to the reduction in number of pregnant women and infants with influenza in Japan. If a higher incidence or maternal mortality was to be applied into our model, the ICER will turn out to be lower than that of base-case estimation.

There are limitations in our study. First, we used cumulative supply of QIV by month to estimate the distribution of pregnant women receiving a shot by month (from October to March). If women received a shot as soon as the vaccine is available or concentrated in October to November, like the situation of 2009 pandemic (60% of pregnant women were vaccinated within 1.5 months), then incremental QALY will increase and ICER will bias to a more favorable one. Second, probabilities of outpatient treatment due to influenza of pregnant/postpartum women and infants were based on data in single season (2017/18 season). There is a possibility of a seasonal variation in influenza severity, where vaccine match may change the parameters substantially. However, the cumulative number of influenza patients who sought for a doctor reported by NIID did not change largely during 2015/16 through 2018/19 season [28]. This suggests that our base-case estimations are reasonable. Third, probability of a pregnant/postpartum women receiving outpatient treatment due to influenza were estimated using data from general population and the probability for infants was estimated by using data of 0–4 years old. If the probabilities for pregnant/postpartum women and infants were higher/lower than our base-case estimations, this will result in lower/higher ICER. Fourth, we assumed no vaccine-induced immunity transfer from mother to child for infants whose mother received flu shot at the last month of her pregnancy, while vaccinated at this timing may contribute to protecting their infants as postpartum-vaccinated [14]. This suggested that ICER of AMVP in Japan may be more favored than our estimation. Fifth, we did not incorporate incidental maternal influenza which may result in immunity to the mother and would provide protection for infants, thus resulting to possibly higher ICER. Sixth, we didn't consider herd immunity in our analysis, however, a pregnant woman who avoided being infected from influenza due to uptake of vaccine may contribute in a reduction in transmission [49]. If this effect was to be considered, the ICER of AMVP can be more favorable.

Despite these limitations, our study has strengths: (1) our model included women who are not pregnant or are with gestational age < 12 weeks by October 1, which previous studies were not able to account, and (2) probabilities of outpatient being received due to influenza for pregnant/postpartum women or their infants varied by calendar time, gestational age, or vaccine status, which is unique from previous studies.

8. Conclusion

AMVP is a key strategy to protect vulnerable neonates and infants too immature to respond effectively to direct vaccination. Our study shows that the vaccination of pregnant women with gestational age ≥12 weeks against seasonal influenza is cost-effective in Japan from both societal and payers' perspectives.

Author's contributions

Aiko Shono and Shu-Ling Hoshi participated in the concept and design of the study, performed the literature searches, acquired the data, analysis and interpretation of the data, and wrote the manuscript. Xerxes Seposo participated in the concept and design of the study and writing of the manuscript. Ichiro Okubo and Masahide Kondo participated in the concept of the study and the interpretation of the data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Swamy GK, Heine RP. Vaccinations for pregnant women. Obstet Gynecol 2015;125(1):212–26.
[2] Poehling KA, Edwards KM, Weinberg GA, et al. The underrecognized burden of influenza in young children. N Engl J Med 2006;355:31–40.
[3] Englund JA, Walter E, Black S, et al. Safety and immunogenicity of trivalent inactivated influenza vaccine in infants: a randomized double-blind placebo-controlled study. Pediatr Infect Dis J 2010;29:105–10.
[4] Vaccines against influenza, WHO position paper – November 2012. https://www.who.int/immunization/position_papers/PP_influenza_november2012_summary.pdf [accessed 20/JAN/2020].
[5] Jit M, Cromer D, Baguelin M, Stowe J, Andrews N, Miller E. The cost-effectiveness of vaccinating pregnant women against seasonal influenza in England and Wales. Vaccine 2010;29:115–22.
[6] Blommaert A, Bilcke J, Vandendijck Y, Hanquet G, Hens N, Beutels P. Cost-effectiveness of seasonal influenza vaccination in pregnant women, health care workers and persons with underlying illnesses in Belgium. Vaccine 2014;32(46):6075–83.
[7] Roberts S, Hollier LM, Sheffield J, Laibl V, Wendel Jr GD. Cost-effectiveness of universal influenza vaccination in a pregnant population. Obstet Gynecol 2006;107(6):1323–9.
[8] Skedgel C, Langley JM, MacDonald NE, Scott J, McNeil S. An incremental economic evaluation of targeted and universal influenza vaccination in pregnant women. Can J Public Health 2011;102:445–50.
[9] Nakai A, Saito S, Unno N, Kubo T, Minakami H. Review of the pandemic (H1N1) 2009 among pregnant Japanese women. J Obstet Gynaecol Res 2012;38(5):757–62.
[10] Sugimura T, Nagai T, Kobayashi H, Ozaki Y, Yamakawa R, Hirata R. Effectiveness of maternal influenza immunization in young infants in Japan. Pediatr Int 2016;58(8):709–13.
[11] Yamada T, Abe K, Baba Y, et al. Vaccination during the 2013–2014 influenza season in pregnant Japanese women. Eur J Clin Microbiol Infect Dis 2015;34(3):543–8.
[12] Yamada T, Kawakami S, Yoshida Y, Kawamura H, Ohta S, Abe K, et al. Influenza 2014–2015 among pregnant Japanese women: primiparous vs multiparous women. Eur J Clin Microbiol Infect Dis 2016;35:665–71.
[13] Ohfuji S, Deguchi M, Tachibana D, Koyama M, Takagi T, Yoshioka T, et al. Estimating influenza disease burden among pregnant women: Application of self-control method. Vaccine. 2017;35:4811–6.
[14] Ohfuji Deguchi M, Tachibana D, et al. Protective effect of maternal influenza vaccination on influenza in their infants: a prospective cohort study. J Infect Dis 2018;217(6):878–86.
[15] Ohfuji S, Deguchi M, Tachibana D, Koyama M, Takagi T, Yoshioka T, et al. Safety of influenza vaccination on adverse birth outcomes among pregnant women: a prospective cohort study in Japan. Int J Infect Dis 2020;93:68–76.
[16] Donzelli A. Influenza vaccinations for all pregnant women? Better evidence is needed. Int J Environ Res Public Health 2018;15(9):2034.
[17] Eli Zimmerman. MDedge News. CDC: Flu vaccine recommendations broaden for pregnant women and children August 29, 2017 https://www.mdedge.com/chestphysician/article/145618/vaccines/cdc-flu-vaccine-recommendations-broaden-pregnant-women-and [accessed 20/JAN/2020].
[18] Benowitz I, Esposito DB, Gracey KD, Shapiro ED, Vázquez M. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. Clin Infect Dis 2010;51(12):1355–61.
[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] Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med 2008;359(15):1555–64.
[21] Blanchard-Rohner G, Meier S, Bel M, et al. Influenza vaccination given at least 2 weeks before delivery to pregnant women facilitates transmission of seroprotective influenza-specific antibodies to the newborn. Pediatr Infect Dis J 2013;32:1374–80.
[22] Jeong S, Jang EJ, Jo J, Jang S. Effects of maternal influenza vaccination on adverse birth outcomes: a systematic review and Bayesian meta-analysis. PLoS ONE 2019;14(8):e0220910.
[23] Ministry of Health, Labour and Welfare. Vital statistics of Japan; 2017. Health and welfare statistics association, Tokyo. Available at: https://www.mhlw.go.jp/toukei/saikin/hw/jinkou/kakutei18/index.html [in Japanese] [accessed 20/JAN/2020].
[24] Jackson LA, Patel SM, Swamy GK, et al. Immunogenicity of an inactivated monovalent 2009 H1N1 influenza vaccine in pregnant women. J Infect Dis 2011;204(6):854–63.
[25] World Health Organization. WHO guide for standardization of economic evaluations of immunization programmes. World Health Organization. Available at https://apps.who.int/iris/handle/10665/69981 [accessed 12/Dec/2019].
[26] Health Service Division, Health Service Bureau, Ministry of Health, Labour and Welfare. (Influenza vaccine. Estimated cumulative supply of influenza vaccine2018/09) Available at: https://www.mhlw.go.jp/content/000410147.pdf [in Japanese] [accessed 20/JAN/2020].
[27] Ministry of Internal Affairs and Communications. Population estimates of Japan. Statistics Bureau, Tokyo; 2018. [accessed 20/JAN/2020].
[28] National Institute of Infectious Diseases (NIID). Numbers of influenza patients weekly surveillance report for the 2018–2019 season [in Japanese].
[29] Ministry of Health, Labor and Welfar. [Nippon Ni Okeru InfuruenzaA (H1N1) No Shibousya No Nenreibetu Uchiwake] Breakdown of influenza A (H1N1) deaths by age/summary in Japan [as of March 30, 2010] https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou04/rireki/100331-03.html [in Japanese] [accessed 20/JAN/2020].
[30] Ferdinands JM, Fry AM, Reynolds S, et al. Intraseason waning of influenza vaccine protection: evidence from the US Influenza Vaccine Effectiveness Network, 2011–12 through 2014–15. Clin Infect Dis 2017;64:544–50.
[31] Belongia EA, Sundaram ME, McClure DL, Meece JK, Ferdinands J, VanWormer JJ. Waning vaccine protection against influenza A (H3N2) illness in children and older adults during a single season. Vaccine 2015;33:246–51.
[32] Fukushima W, Ohfuji S, Deguchi M, et al. Effectiveness of an influenza A (H1N1) 2009 monovalent vaccine among Japanese pregnant women: a prospective observational study assessing antibody efficacy. Vaccine 2012;30(52):7630–6.
[33] Black SB, Shinefield HR, France EK, Fireman BH, Platt ST, Shay D. Vaccine Safety Datalink Workgroup. Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. Am J Perinatol 2004;21(6):333–9.
[34] Madhi SA, Cutland CL, Kuwanda L, et al. Maternal Flu Trial (Matflu) Team. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med 2014;371(10):918–31.
[35] Demicheli V, Jefferson T, Ferroni E, Rivetti A. Di Pietrantonj. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2018.
[36] Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis 2012;12(1):36–44.
[37] O'Brien BJ, Goeree R, Blackhouse G, Smieja M, Loeb M. Oseltamivir for treatment of influenza in healthy adults: pooled trial evidence and cost-effectiveness model for Canada. Value Health 2003;6(2):116–25.
[38] Sruamsiri R, Ferchichi S, Jamotte A, Toumi M, Kubo H, Mahlich J. Impact of patient characteristics and treatment procedures on hospitalization cost and length of stay in Japanese patients with influenza: a structural equation modelling approach. Influenza Other Respir Viruses 2017;11(6):543–55.
[39] Xu J, Zhou F, Reed C, Chaves SS, Messonnier M, Kim IK. Cost-effectiveness of seasonal inactivated influenza vaccination among pregnant women. Vaccine 2016;34(27):3149–55.
[40] Myers ER, Misurski DA, Swamy GK. Influence of timing of seasonal influenza vaccination on effectiveness and cost-effectiveness in pregnancy. Am J Obstet Gynecol 2011;204(6 Suppl 1):S128–40.
[41] Beigi RH, Wiringa AE, Bailey RR, Assi TM, Lee BY. Economic value of seasonal and pandemic influenza vaccination during pregnancy. Clin Infect Dis 2009;49(12):1784–92.
[42] Qlife. Average vaccination costs of influenza vaccine https://news.mynavi.jp/article/20181025-712860/ [accessed 20/JAN/2020].
[43] Kaji M, Kuno H, Oizumi K. Costs of influenza therapy. Kansenshogaku Zasshi 2001;75(6):460–3 [in Japanese].
[44] Ministry of Health, Labour and Welfare. The 22th life tables. Health and Welfare Statistics Association, Tokyo; 2012 [in Japanese] [accessed 20/JAN/2020].
[45] Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 4th ed. Oxford: Oxford University Press; 2015.
[46] Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness?. Health Econ 2010;19(4):422–37.
[47] World Health Organization. WHO guide for standardization of economic evaluations of immunization programmes. Geneva, Switzerland: WHO Document Production Services; 2008 [accessed 20/JAN/2020].
[48] Hoshi SL, Seposo X, Okubo I, Kondo M. Cost-effectiveness analysis of pertussis vaccination during pregnancy in Japan. Vaccine 2018;36:5133–40.
[49] Yamin Dan, Gavious Arieh. Incentives' effect in influenza vaccination policy. Manage Sci 2013;59(12):2667–86.