Vaccine 36 (2018) 5133–5140

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness analysis of pertussis vaccination during pregnancy in Japan

Shu-ling Hoshi [a,*], Xerxes Seposo [b], Ichiro Okubo [c], Masahide Kondo [a]

[a] Department of Health Care Policy and Health Economics, Faculty of Medicine, University of Tsukuba, 1-1-1, Tennoudai, Tsukuba, Ibaraki 3058577, Japan
[b] Department of Environmental Engineering, Environmental Health Division, Kyoto University, Nishikyo-ku, Kyoto 6158246, Japan
[c] Yokohama City Institute of Public Health, 7-1, Tomiokahigashi 2-chom, Kanazawa-ku, Yokohama City 236-0051, Japan

ARTICLE INFO

Article history:
Received 8 February 2018
Received in revised form 12 July 2018
Accepted 13 July 2018
Available online 21 July 2018

Keywords:
Cost-effectiveness
Economic evaluation
Pertussis
Tdap
DTaP
Vaccination
Quality-adjusted life year

ABSTRACT

Background: Both re-emergence of pertussis outbreak among adolescents/adults and recent approval of the extended use of DTaP vaccine for boosting adolescents/adults against pertussis in Japan, have raised the possibility of using aP-containing vaccine in pregnant women to protect neonates and unvaccinated infants. There is a need, therefore, to evaluate the value for money of such possibility.
Methods: We evaluated the cost-effectiveness of conducting antepartum maternal vaccination (AMV) strategy in Japan. Considering the duration of vaccine effectiveness for infant (single year) and for mother (multiple years), the decision tree model and Markov model was adapted for infant and mother, respectively. Incremental cost-effectiveness ratio (ICER) compared with current no AMV strategy from societal perspective were calculated. The 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 ¥6000/US$54.5. Markov model for mothers with one-year cycle runs up to year four after vaccination, based on the waning of vaccine effectiveness. Infant who survived from pertussis was assumed to live until to his/her life expectancy.
Results: AMV strategy reduces disease treatment costs, while the reduction cannot offset the vaccination cost. Incremental QALYs were at 0.0002802, among them 79.5% were from infants, and others from mothers. ICER was ¥9,149,317/US$83,176 per QALY gained. One-way sensitivity analyses identified that the incidence rate and costs per shot were the two main key variables to impact the ICER.
Conclusion: We found that vaccinating pregnant women with aP-containing vaccine to prevent neonatal and unvaccinated infants from pertussis-associated disease in Japan can be cost-effective from societal perspective, under the WHO-suggested "cost-effective" criteria (1 to 3 times of GDP). Pertussis is expected be designated as a notifiable disease in 2018, re-analysis should be conducted when straightforward incidence data is available.

1. Introduction

Pertussis is an acute respiratory disease caused by the bacterium *Bordetella pertussis*. It is a highly contagious disease transmitted through respiratory droplets and is usually difficult to be differentiated from similar pathological conditions such as prolonged cough or common cold [1]. These similar pathological manifestations lead to underdiagnoses, thus leaving a pool of patients harboring the infection, which can serve as a source of future infections [1,2]. Pertussis can affect people of all ages, but with particularly severe complications among neonates and unvaccinated infants, thus making the prevention of such infection among the said vulnerable population of prime importance [1,2]. Even after the introduction of vaccination programmes and the achievement of high vaccination coverage, pertussis, which is endemic to all countries, have epidemic cycles occurring every 2–5 years [1].

Strategies for preventing pertussis among young infants before they commence their vaccinations at 2 or 3 months of age include: (1) booster doses in adolescents or adults (though there is yet have a substantial evidence that these programmes have significant impact) [1]; (2) cocooning strategy, i.e., vaccinating the infant's close contacts (beneficial effects of this strategy are inconsistent) [1]; (3) antepartum maternal vaccination (AMV) strategy, i.e., giving aP-containing vaccine in the third trimester in every pregnancy to prevent severe infant morbidity and mortality from pertussis during the narrow window before receiving their first dose of

* Corresponding author.
E-mail address: hoshi@hcs.tsukuba.ac.jp (S.-l. Hoshi).

https://doi.org/10.1016/j.vaccine.2018.07.026
0264-410X/

vaccine. Though AMV is relatively new [3], convincing and robust evidences have consistently indicated that it will not only reduce the infection among mothers, but also protect infants through the transfer of maternal antibody [1,4,5]. High-income countries, such as United States, the United Kingdom, Belgium, Ireland, Italy, Portugal, and New Zealand, where pertussis immunisation programmes have existed for a long time have already been implementing AMV [4,6].

In Japan, DTaP vaccine was introduced in 1981 and pertussis has been controlled by means of a vaccination schedule of three primary doses (at 3, 4, 5 months) and a single booster dose (18–23 months). Vaccine coverage of three primary doses of DPT-IPV in 2014 were at 99.2%, 99.1%, and 99.1%, in the first, second and third doses, respectively [7]. Similar to other countries, there is a re-emergence of pertussis outbreak in adolescents and adults, raising topics about pertussis control through various strategies. Currently, national initiatives have paved way in addressing pertussis control. In February 2016, the Ministry of Health, Labour and Welfare (MHLW) approved the extended use of DTaP as a booster for both adolescents and adults. This has then led to the possibility of using DTaP in pregnant women [8]. Taking into account the current progress in pertussis control, our study aims to estimate the value for money of AMV strategy by using aP-containing vaccine in Japan, assuming that in the future, there may be a need to consider its implementation.

2. Method

We conducted a cost-effectiveness analysis to evaluate the cost-effectiveness of the vaccination programme. The model was constructed by using TreeAge Pro, 2017, TreeAge Software.

2.1. Literature search

We searched the various databases for the parameters which were included in the modeling. Studies pertaining to epidemiology and prognosis of pertussis-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. Though we didn't limit the literature search to recently published journal articles, we selected, as much as possible, the robust ones suitable to our model, particularly data relevant to the epidemiology and prognosis of the disease, together with the vaccine effectiveness and the related utilities.

2.2. Programme

Our study estimated the value for money of AMV strategy in Japan by comparing AMV strategy with current no AMV strategy.

2.3. Models and variables

Two cohorts were followed via a decision tree and Markov model; one for the pregnant women and the other for their new born babies (given that maternal pertussis antibodies protect the newborn in the first 3 months of life). The decision tree model describing the courses for individuals started from a decision node, which were consequently followed by chance nodes with regard to the following circumstances (Fig. 1): (1) vaccinated/not vaccinated, (2) perinatal mortality/live birth, (3) pertussis contraction/no pertussis contraction, and (4) clinical courses after the contraction. Adverse effects of vaccination were not incorporated based on reports from large clinical trials and from post-marketing surveys [9,10].

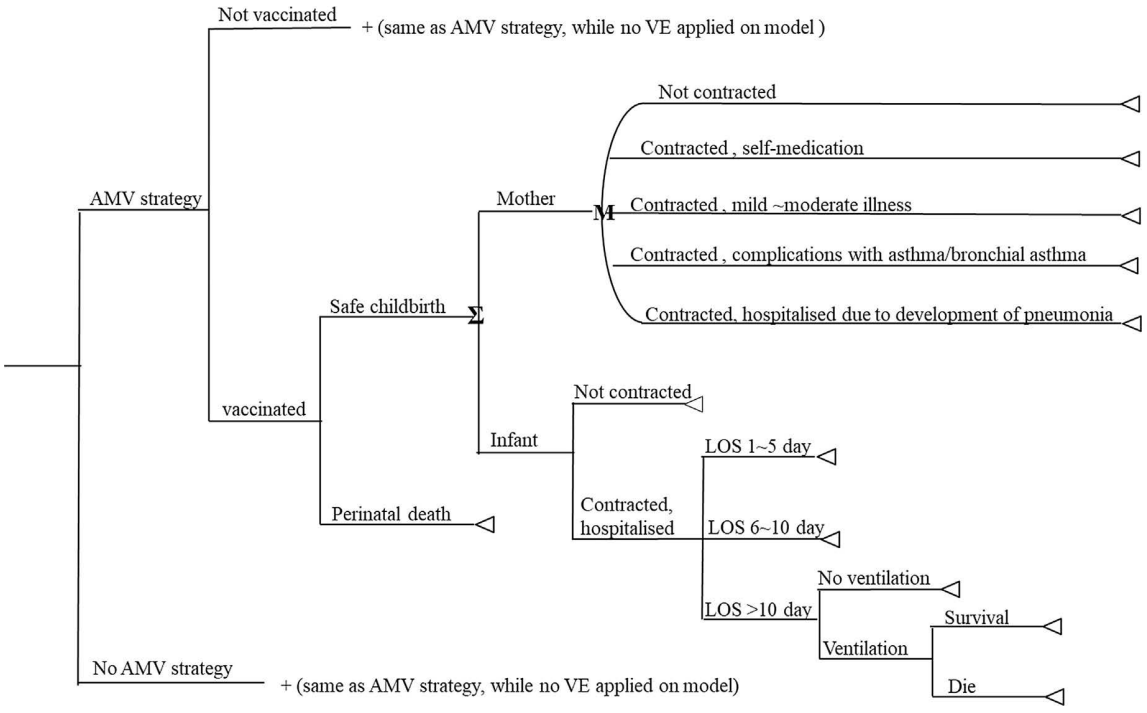


Fig. 1. Model. M: Markov model; Σ: Sum of both mother's and infant's results; LOS: Length of stay (in hospital).

Probability that a pregnant woman decided whether to uptake the vaccine or not, at 0.50, was based on influenza vaccine coverage among pregnant women in Japan in 2009 [11]. The probability that a baby was not safely delivered, at 0.0026, was based on the perinatal mortality in Japan in 2017 [12]. When perinatal mortality occurred, the benefit of vaccination will only go to the mothers.

The decision tree model continued for the infant's branch, because as the infant reaches the vaccination age, vaccine effectiveness (VE) from AMV strategy will no longer be considered, and the probability of being infected by pertussis will not be different between children born to vaccinated or non-vaccinated mothers. An infant who survived from pertussis was assumed to live until to his/her life expectancy [13]. In Japan, since pertussis incidence rate among infants aged < 3 m.o. is not available, we estimated the incidence rate from Suge et al. [14], at 139.6/100000 person-year (as seen in Table 1), instead.

We assumed that the pertussis cases aged <3 m.o. were all hospitalised [15]. The hospitalised infants were further divided into three groups by length of stay (LOS): (a) short-LOS group (probability of belonging to the group at 20.9%), (b) medium-LOS group (at 49.5%), and (c) long-LOS group (at 29.7%) [14]. LOS of each group is shown in Table 2. Among long-LOS group, 20.6% needed mechanical ventilation [14,16,17]. The fatality rate for those who required ventilation was assumed at 7.14% [17].

For mother's branch, a Markov model with one-year cycle was applied, since VE was expected to continue to the fourth year after vaccination [18]. Incidence rate of pertussis for the mother was assumed to be the same with that of the infant's [19]. Five mutually exclusive health states were used to describe the courses that a mother may follow (shown in Fig. 1). We assumed that 0.50% of mothers were hospitalised due to development of pneumonia based on a study by Miyashita et al. [20]. Miyashita et al. reported that among the 183 patients with laboratory-confirmed pertussis (by serology and polymerase chain reaction), only 0.50% was hospitalised, whereas percentage of hospitalisation among 1132 non-laboratory confirmed pertussis was at 0.80%; the study was conducted in a medical university hospital from 2005 to 2012 (with participants aged 16–77). There is a possibility that proportion of hospitalisation was underestimated because the authors excluded patients with underlying diseases that caused persistent cough. Taking all of these into consideration, we conservatively assumed the 0.50% hospitalisation rate in base-case analysis and used 0.80% for sensitivity analysis. Furthermore, we also assumed that 35.7% had complications with asthma/bronchial asthma and other mild-moderate illnesses based on study by Nogami et al. [21]. Nogami et al. reported that 5 of 14 loop-mediated isothermal amplification (LAMP) method and pertussis toxin antibody test of confirmed pertussis adult cases developed asthma/bronchial asthma, while only 5.3% (1/19) of non-confirmed cases developed asthma/bronchial asthma. We adopted the 35.7% in our base-case analysis and used 18.1% (6/33) in sensitivity analyses. Due to the data unavailability, we assumed that among patients who had mild-moderate illnesses, 80% seek medical treatment from a physician, while 20% treated themselves by purchasing over-the-counter (OTC) medication.

2.4. Vaccine effectiveness

VE in reducing contract pertussis for infants born to vaccinated mothers was assumed at 91% (86.5–94.4%) [4,5], preventing infants with pertussis from hospitalisation was at 58% (15–80%) [22], and preventing infant from death was at 95% [23]. Since there is no straightforward data related to the VE of preventing a vaccinated mother from contracting the disease, we adopted the VE estimates from two studies, which reported efficacy of aP-containing vaccine among adolescents/adults; namely, (1) Ward et al.'s RCT (reported a VE at 92% (32–99%) for a 22-month median follow-up duration among 18 wards), and (2) Koepke et al.'s comparison of VE between different Tdap brands (indicated that by the 4th year of Tdap receipt, no significant VE can be observed) [18]. In our study, VE in preventing a vaccinated mother from contracting pertussis was assumed to be at 92% (32–99%) in the 1st year and was assumed to linearly decrease to 0% within four years [18,24].

2.5. Health outcomes and end point

Incremental cost-effectiveness ratio (ICER) of AMV programme compared with no immunisation programme was calculated. ICER is defined as difference in cost between immunisation programme and no immunisation programme, divided by the difference in their effectiveness in terms of quality-adjusted life year (QALY). QALY, which takes into account the utility weights and the duration of illness, was estimated by assigning transition probabilities and utility weights from literature to the Markov model. The utility

Table 1
Estimation of infant pertussis hospitalisation incidence rate.

	Prefectures						
	Mie	Fukuoka	Chiba	Okinawa	Kouchi	Fukusima	Total
Original data from study of Suge et al.[a] (January 2009–December 2013)							
(a) Number of pertussis hospitalised patients age < 15 y.o.	22	249	57	78	24	35	465
(b) Percentage of hospitalised patient age < 3 m.o.	59%	57%	61%	49%	54%	57%	56%
(c) Number of pertussis hospitalised patients age < 3 m.o. (=a × b)	13	142	35	38	13	20	260
Number of birth from vital statistic							
2009	15,614	46,084	51,839	16,744	5415	16,326	152,022
2010	15,262	46,818	51,633	17,098	5518	16,216	152,545
2011	15,080	46,220	50,379	16,918	5244	15,072	148,913
2012	14,729	45,815	48,881	17,074	5266	13,770	145,535
2013	14,514	45,897	48,343	17,209	5266	14,546	145,775
(d) Total number of birth (2009 ~ 2013)	75,199	230,834	251,075	85,043	26,709	75,930	744,790
Person-year (<3m.o.) =(3/12) * (d)	18,800	57,709	62,769	21,261	6677	18,983	186,198
Incidence rate/10000 person-year							139.9 (=100000 × 260/186198)
Incidence rate/100000 person-month							11.66

[a] Suge et al.' study [14] is a complete enumeration retrospective survey from all the hospitals located in six prefectures of Japan, which reported 465 pertussis patients aged < 15 years old, who were hospitalised during January 2009 to December 2013, among them 56% (260 patients) were aged < 3 months.

Table 2
Variables.

Probability used at each chance node	Maternal	Infant	Distribution used in PSA	Reference
Probability for a pregnant woman to uptake the vaccine; %	50	–	constant	[11]
Probability that a baby was safely delivered (perinatal mortality); %	0.26	–	constant	[12]
Probabilities of a non-vaccinated mother or her infant to contract pertussis; per 100,000	139.6 (119.0–519.6)		Uniformed	[14,19,27]
Probabilities of a non-vaccinated mother/infant to be hospitalised after contracting pertussis;%	0.50	100		[15]
Probabilities of a hospitalised infant who's LOS* was 1–5 days (mean: 3 days); %	–	20.9	[c]	[14]
Probabilities of a hospitalised infant who's LOS was 6–10 days (mean: 8 days); %	–	49.5 (39.6–59.4)	Uniformed	[14]
Probabilities of a hospitalised infant who's LOS was >10 days (mean: 15 days); %	–	29.7 (23.8–35.6)	Uniformed	[14]
Probability of an infant pertussis patient with LOS >10 days, require mechanical ventilation treatment; %	–	20.6 (16.8–25.1)	Uniformed	[14,16,17]
Probability of an infant pertussis patient dying in NICU; %		7.14 (3.10–8.60)	Uniformed	[17]
Probabilities of a non-vaccinated mother developed pneumonia after contracting pertussis; %	0.5			[20]
Probabilities of a non-vaccinated mother developed asthma/bronchial asthma after contracting pertussis; %	35.7	–		[21]
Probabilities of a non-vaccinated mother ill mild ∼ moderate visted a doctor after contracting pertussis; %	80.0	–		assumed
Probabilities of a non-vaccinated mother ill mild ∼ moderate treated herself by purchasing OTCs; %	20.0	–		assumed
Life expectancy for new born (before discounting[a])	–	Mlae:79.58 Female: 86.32	constant	[13]
Percentage of male new born		0.513	constant	[12]
Vaccine effectiveness				
Protecting from contracting pertussis;%	92.0 (waning to 0 by 4 years)	91 (32–99)	uniform	[18,24,4,5]
Protecting infant with pertussis from hospitalisation;%	–	58.0 (15–80)	uniform	[22]
Protecting hospitalised infant from death;%	–	95.0 (76–100)	uniform	[23]
Reducing LOS; days	–	3 (2–4)	uniform	[22]
Reducing cough days	5 (4–6)		uniform	[26]
Utility weights				
Infant: hospitalised	–	0.58 (SD 0.37)	Normal	[25]
Infant: mechanical ventilation	–	0.29 (0.23–0.35)	uniform	[25]
Mother: mild ∼ moderate illness	0.85 (0.696–0.99)	–		[25]
Mother: hospitalised	0.82 (SD 0.3)	–	Normal	[25]
Mother: asthma	0.81 (SD 0.30)	–	Normal	[25]
LOS for short-LOS group; days	–	5 (4–6)	Triangle	assumed
LOS for median-LOS group;days	–	8 (7–9)	Triangle	assumed
LOS for long-LOS group; need not ventilation; days	–	9.5 (SD 4.4)	Normal	[16]
LOS for long-LOS group; need ventilation; days	–	26 (SD 9.6)	Normal	[16]
Average duration of assisted ventilation; days	–	12.5 (SD 7.4)	Normal	[16]
Mean cough days for none vaccinated mother/their infant; days	55 (45–120)	60 (45–120)	Triangle	[20.21]
Mean cough days for vaccinated mother/their infant; days	Half of mean cough days for none vaccinated mother/their infant			
*Costs**				
Vaccination	¥6,000 (¥2000-¥10000)	–	constant	assumed
Treatment costs				
Infant: per hospitalised day	–	¥46,010(±20%)	Gamma[b]	[36]
Infant: per NICU/PICU day	–	¥147,800(±20%)	Gamma[b]	[37]
Mother: OTC	¥10,000 (±20%)	–	Gamma[b]	assumed
Mother: outpatient	¥33,901	–	Gamma[b]	[36]
Mother: asthma/bronchial asthma	¥100,000	–	Gamma[b]	[36]
Mother hospitalised due to develop of pneumonia	¥116,304	–	Gamma[b]	[36]

LOS: Length of stay (in hospital); OTC: Over the counter medicine; NICU: Neonatal intensive care unit; PICU: Perinatal intensive care unit; PSA: probabilistic sensitivity analysis.
Numerical values shown in parentheses are, lower- and upper- values, Stand Deviation (SD) used for sensitivity analyses.
[a] Future cost and health benefit occurred after fist year were discounted (3% yearly) by using $P = F_0 + F_1/1.03 + F_2/1.03^2 + F_3/1.03^3 + \ldots$ Where P = present value, Fn = future cost or health benefit at year n.
[b] Probability density plots of gamma distributions: $\alpha = 1$, $\beta = \text{cost}/\text{cost}^2$.
[c] This variable are set as (1− Probabilities of a hospitalised infant whose LOS was 6–10 days – Probabilities of a hospitalised infant who's LOS was >10 days.

weights for mother/infant in different health states were from Lee et al. [25], which were frequently cited in previous studies. The literature search did not identify any study reporting the utility of patients who were in need of assisted ventilation, so it was assumed to be half of that of hospitalised infants. LOS for infant born to vaccinated mother was assumed to be 3 days shorter than those born to unvaccinated mothers [22]. The mean cough days for unvaccinated mothers and infants were assumed to be 55 (45–120 days) [20,21] and 60 days, respectively, while those for vaccinated mothers and their infants were assumed to be half of the unvaccinated and their infants [26].

We estimated ICER from societal perspective, which in this case is also payer's perspective because maternity leave (six weeks ahead of expected date of birth to eight weeks after delivery for all the female employees) and 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.

2.6. Costs

The amount of direct payments to health care providers by government, municipalities, vaccinees, patients and third party payers was estimated as costs, while non-direct medical costs related to the immunisation programme were not included, because we assumed that the vaccination programme will be built within the public health services routine.

Vaccination costs per aP-containing shot (included doctor's fee for medical advice and technical fee for administering) was assumed at ¥6000 (US$54.5) based on: (1) costs per Tdap shot, though not available in Japan, ranged from US$14.6∼$57.6 according to previous studies [19,27–34] and (2) cost per DTaP in Japan is around ¥5500 (US$50.0) [35]. Treatment costs for hospitalised infant were estimated as cost per diem multiplied by hospital days. For infants, cost per diem of acute upper respiratory tract infection for patients aged 0–4 year old was assumed at ¥46,014 (US$418.3) based on the data published by MHLW in 2015 [36]. Cost per diem for patient who needs ventilation was assumed at ¥147,600 (US $1341.8; including NICU/PICU fee) based on medical fee schedule published in 2015 [37]. Cost for those who died after treatment, assumed as cost per diem for patient who needed ventilation multiplied by assisted ventilation days (12.5 ± 7.4 days), was from Kishimoto et al., which reported the treatment process of 46 severe infantile pertussis cases [16]. For mothers, ¥10,000 (US$90.9) per case for patients who purchased OTC, ¥30,000 (US$272.7) per case (¥4843/visit × 7 visits)for those who sought a doctor, and ¥100,000 (US$909.1) per case for those who developed bronchial asthma. For those who were hospitalised due to the development of pneumonia, cost was estimated as costs per diem multiplied by hospital days (¥38,768/US$352.4 × 3 days) based on data published by MHLW in 2015 [36]. Costs per diem used in this study were all reported at 2015, which were the most recently available data.

In this study, we used the average currency ratio from 2017 January to 2018 January, at 1US$ = ¥110.

2.7. Discounting

Costs and outcomes occurring over 1 year were discounted at an annual rate of 3% [38].

2.8. Sensitivity analyses

To appraise the ICERs' stability with the assumptions made in our economic model, and to explore the impact of each variable relative to each other, we performed one-way sensitivity analyses with all the variables utilised in this study. We also performed a two-way sensitivity analyses using the top two variables which changed the ICER the most. Probabilistic sensitivity analyses (PSA) [38,39], i.e., 1000 Monte Carlo simulations, were also conducted. Results of the upper- and lower- limits as well as distributions for PSA are reported in Table 3.

2.9. Cost-effectiveness threshold

Since there is no established threshold in judging the cost-effectiveness of public health programmes in Japan, a willingness-to-pay threshold at ¥5,000,000 (US$45,455) per QALY gained was utilised; a suggested threshold for evaluating healthcare interventions [40]. Also, WHO suggests a "cost-effective" criterion at 1 to 3 times of GDP [41]. These criteria were used in determining whether the immunisation programme was cost-effective or not.

3. Results

3.1. Results of base-case analysis

Table 3 shows the results of base-case analyses. When comparing AMV strategy with current no AMV strategy, estimated average incremental QALYs were at 0.0002802, among them 79.5% (0.0002227 QALYs) were from infant, and remaining 20.5% were from mother. Though AMV strategy reduces disease treatment costs, the reduction cannot offset the vaccination costs. Estimated incremental cost-effectiveness ratio (ICER) were at ¥9,149,317 (US $83,176)/QALY gained.

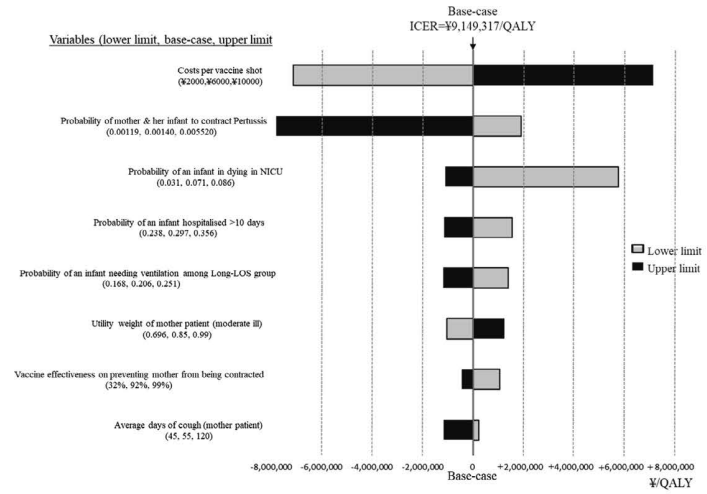
3.2. Results of sensitivity analyses

In Fig. 2-1, we can observe the eight variables which changed the ICER to be greater than ¥1,000,000 (US$9091)/QALY. Two-way sensitivity analyses on two key variables (Table 4, Fig. 2-2), i.e., costs per shot and probabilities of an infant aged < 3 m.o. from a non-vaccinated mother to contract pertussis, showed that if we adopt a ¥10,000,000 (US$90,909)/QALY as a criterion for cost-effectiveness, AMV strategy will be cost-effective regardless of the incidence rate of infant pertussis when cost per shot ≤¥5,500 (US$50.0). While if we adopt ¥5,000,000 (US$45,454.5)/QALY as a criterion, AMV strategy will only be cost-effective when cost per shot is ≤¥3,000 (US$27.3). Fig. 2-3 shows the cost-effectiveness acceptability curve (CEAC) of AMV strategy compared to current no AMV strategy. Among 1000 ICERs produced by Monte Carlo simulations, the probabilities that ICER is under ¥5,000,000 (US $45454.5) and ¥10,000,000 (US$90909.1) per QALY gained was at 65.4% and 92.3%, respectively. Mean ICER was ¥4,595,055 (SD = ¥3,563,788) or US$41,773 (SD = US$32,398) per QALY.

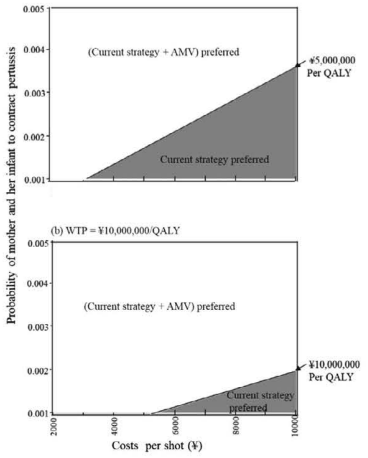
Table 3
Results: cost, incremental cost effectiveness and incremental effectiveness per mother and/or per infant, and ICER of base-case analysis.

	Cost		Incremental cost		Effectiveness	Incremental effectiveness	ICER	
Strategy	(¥)	(US$)	(¥)	(US$)	(QALYs)	(QALYs)	(¥/QALY)	(US$/QALY)
Total (mother and infant)								
current strategy	981	8.9			35.341758			–
current strategy + AMV	3545	32.2	2564	23.3	35.342038	0.0002802	9,149,317	83175.6
Mother								
current strategy	305	2.8			3.9825251			
current strategy + AMV	3188	29	2883	26.2	3.9825846	0.0000575		
Infant								
current strategy	675	6.1	319	2.9	31.35923			
current strategy + AMV	356	3.2	0	0	31.35946	0.0002227		

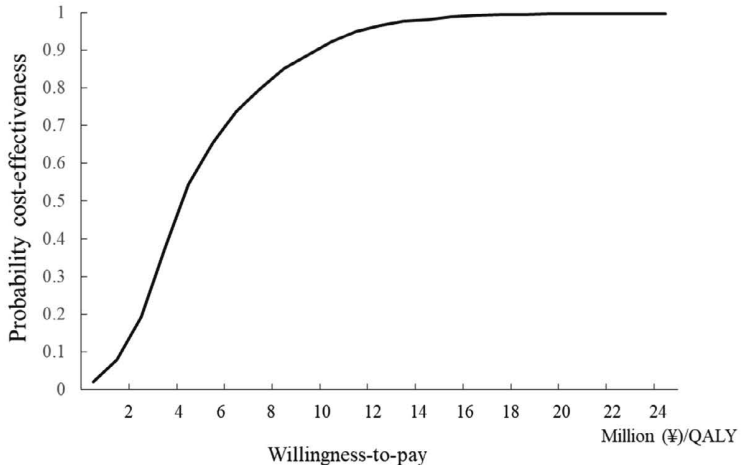
AMV: Antepartum Maternal Vaccination.
QALY: Quality Adjusted Life Year.
ICER: Incremental cost-effectiveness ratio.



(1) One-way sensitivity analysis (Tornado diagram showing the eight variables which changed the ICER to be larger than ¥1,000,000/QALY)



(2) Two-way sensitivity analyses (cost per shot vs. probability to contract pertussis)



(2) PSA: cost-effectiveness acceptability curve (CEAC).
Among 1,000 ICERs produced by Monte Carlo simulations, the probabilities that ICER is under ¥5,000,000 (US$45,454.5)/ ¥10,000,000 (US$90,909.1) per QALY gained was at 65.4%/92.3% when the costs of per course of vaccination were at¥60,000 (US$54.5).

Fig. 2. Sensitivity analyses (Current strategy + AMV vs. current strategy): (2-1) One-way sensitivity analyses, (2-2) Two-way sensitivity analyses, and (2-3) Probabilistic sensitivity analyses (PSA) QALY: quality adjusted life year. ICER: incremental cost-effectiveness ratio (¥/QALY). WTP: willingness-to-pay.

Table 4
Results (ICERs) of two-way sensitivity analyses (ICER = ¥/QALY).

	Incidence rate of pertussis in infant and mother, respectively				
Costs per shot	0.001	0.002	0.003	0.004	0.005
¥2000	3,438,545	941,905	109,841	Dominant*	Dominant
¥3000	5,936,300	2,191,228	943,019	319,026	Dominant
¥4000	8,434,056	3,440,551	1,776,198	944,132	444,982
¥5000	10,931,811	4,689,874	2,609,376	1,569,239	945,245
¥6000	13,429,566	5,939,196	3,442,555	2,194,345	1,445,508
¥7000	15,927,321	7,188,519	4,275,733	2,819,451	1,945,770
¥8000	18,425,076	8,437,842	5,108,912	3,444,557	2,446,033
¥9000	20,922,831	9,687,165	5,942,090	4,069,664	2,946,296
¥10,000	23,420,586	10,936,488	6,775,269	4,694,770	3,446,559

* Dominant: When comparing AMV strategy with current no AMV strategy, AMV strategy gained more QALYs with less cost.

4. Discussion

We conducted the first cost-effectiveness analysis in Japan comparing AMV strategy (with aP-containing vaccine) to current no vaccination for pregnant women. The purpose of AMV is mainly to prevent infant < 3 m.o. from contracting pertussis. Results showed that ICER of AMV strategy was under the WHO-suggested "cost-effective" criterion at 1 to 3 times of GDP (¥11,000,000 or US$100,000 in Japan) [41]. One-way sensitivity analyses showed that costs per shot and incidence rate of infant

pertussis were the two key variables which have large impacts on the results. Two-way sensitivity analyses indicated that the upper limit of the cost per shot to gain one QALY under ¥5,000,000 (US $45,455) and ¥10,000,000 (US$9091), regardless of the incidence rate of infant pertussis, were at ¥3000 (US$27.3) and ¥5500 (US $50.0), respectively. PSA show that the probabilities of AMV strategy to be under ¥5,000,000 (US$45454.5) and ¥10,000,000 (US $90909.1) per QALY are 65.4% and 92.3%, respectively. Mean ICER (¥4,595,055 or US$41773.2 per QALY) derived from PSA was favoured than that of deterministic analysis (¥9,149,317 or US $83175.6 per QALY) due to the usage of a relatively high upper limit of incidence rate of pertussis, i.e., 519.6/100,000 person-year; adopted from van Hoek et al. [19].

Since our study is the first study which evaluated the value for money of AMV strategy with aP-containing vaccine in Japan, no comparison can be done within same healthcare setting, hence, we compared our study with seven previous studies from overseas [19,27,30–34]. Reports by Atkins et al. (USA), Sartori at al. (Brazil) and Westra et al. (Netherland) concluded that AMV strategy was cost-effective [30–32]. While, van Hoek et al. (England) reported that AMV strategy gained one QALY at £16,856∼£42,070 depending on the incidence [19]. Lunger et al. (Netherland) reported an ICER of €126,000/QALY and discussed that the high ICER may partly be due to the assumption about the lower disease burden. Terranella et al. (USA) reported an ICER at US$414,523/QALY; the resulting high ICER may partly be due to the high vaccine cost US$57.6/shot (the highest one among the previous studies). Fernández-Cano et al. (Spain) reported a benefit-to-cost ratio of 0.15 and mentioned that additional CEA studies are needed. Analytic time horizon for mother in previous studies as well as in our study was more than 1 year, while this variable in study of Fernández-Cano et al. was set at 1 year only; this assumption may contribute to the low benefit-to-cost ratio. Our results suggested that AMV strategy in Japan can be potentially cost-effective, while the result is largely depending on the incidence. The incidence rates (per 100,000 person-month) of infant pertussis from previous studies were: 10.8 (age < 5 m.o.) in Lugner et al.'s study, 7–43.3 (age < 3 m.o.) in Van Hoek et al.' study; 5.54 (age < 12 m.o.) in Satori et al.'s study, 9.9 (age < 2 m.o.) in Fernandez-Cano et al.'s study; 12.4 (age < 1 m.o.), 18.9 (age 1 m.o.), 15.3 (age 2 m.o.) in Terranella et al.'s study; 9.0 (age < 1 m.o.), 17.7 (age 1 m.o.), and 23.4 (age 2 m.o.) in Westra et al.'s study. While in our study we observed that it was at 11.7 (<3 m.o.), which is comparatively low when compared to those used in previous studies. Incidence rates in all the seven previous studies were from the notifiable diseases' surveillance system of each country. Underreporting related to incidence in infants has been discussed in all the previous studies, most studies concluded that there were minor underreporting in infants' incidence because pertussis usually leads to disease severe enough to be recognise among infants [19,27,30–34]. Pertussis in Japan is defined as a sentinel-reported disease, therefore, at this point we have no way of finding whether our estimated results are under-reported or not. Costs per vaccination is another key variable which impacts the results largely. Among previous studies, cost per vaccination is between ¥1606∼¥6336 (US$14.6–57.6), which, in our study, was set at ¥6000 (US$54.5).

Our study has certain limitations, namely: (1) One-way sensitivity analyses revealed that pertussis incidence rate is a variable which has strong impact on ICER. In Japan, pertussis is not a notifiable disease, therefore we estimated the incidence rate based on a complete enumeration retrospective survey from all the hospitals located in six prefectures in the country. As discussed above, our estimated incidence rate is comparatively low when compared to those used in previous studies. Until the disease is assigned as a notifiable disease, there is no way to know whether the figure is overestimated or under estimated. From January 2018, pertussis is expected to be assigned as a notifiable disease, re-analysis should be conducted when incidence data is available. (2) Since we are not able to further characterise infant health outcome according to pneumonia or other pertussis-related complications, we used the costs of upper respiratory infection to estimate the hospitalised instead; this might result to the underestimation of pertussis cost. (3) We didn't define other strategies, which also aims at reducing the incidence among infant as alternative strategies. There are three previous studies which compared AMV with cocooning/neonatal strategy. Among them, two reported that AMV strategy is favourable than cocooning/neonatal strategy [31,34], while Lugner et al. reported that cocooning strategy is favourable than AMV strategy [33]. Lugne et al. assumed that in cocooning, all new mothers would be vaccinated only if they had not received the vaccine in the previous 5 years, while in AMV strategy all pregnant women had to be vaccinated during each pregnancy, this assumption makes the cocooning strategy to have lower vaccination cost than AMV strategy, which led to the result of cocooning being favourable than AMV. (4) The utility weights were cited from overseas which would cause uncertainty to the result, however, sensitivity analyses revealed that the impact of these utility weights were not significantly large. (5) Though vaccine coverage are high in Japan with three primary doses reaching 90%, the delays of vaccination, which happened in some cases would leave infants at a longer vulnerable age with less protection than anticipated [42]. It is possible that transplacental maternal antibodies or the antibody through breastfeeding could protect those infants [43]. (6) We only took into account the benefits of the protection of pertussis without considering additional benefits, which can be expected if combination vaccine was to be used. (7) An ecological study reported that increased DTaP immunisation coverage is associated with decreased sudden infant death syndrome (SIDS) mortality [44]. Another study reported that among SIDS mortality, 5.1% was caused by pertussis [45]. If these additional benefits were to be included, ICERs may be improved.

In February 2016, the MHLW approved the extended use of DTaP for boosting adolescents and adults [6]; a DTaP-IPV dose to replace current one Td dose for adolescents ageing 11–12 y.o. is now under consideration. Several countries have implemented booster dose for adolescents to control the transmission, however, vaccinating adolescents might increase the average age of re-infection resulting to more susceptible young mother due to the waning of the VE of the acellular vaccine to protect against the transmission of pertussis [19]. Taking into account the current circumstances in pertussis control, in the near further, Japan may need to consider the implementation of AMV strategy to protect infants from pertussis during the narrow window before receiving their first dose of vaccine. Our study suggests that in Japan using aP-containing vaccine in pregnant women has the potential to be cost-effective.

5. Author's contributions

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

Conflict of interest

None.

Sponsors role

None.

Acknowledgements

This study was supported by a research grant for Research on Emerging and Re-emerging Infectious Diseases, Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare, Japan.

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