Original article

Title:

Economic evaluation of vaccination programme of 13-valent pneumococcal conjugate vaccine to the birth cohort in Japan.

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1. Introduction

The 7-valent pneumococcal conjugate vaccine (PCV-7) was firstly approved in the USA in 2000 for the prevention of diseases caused by Streptococcus pneumoniae (pneumococcus) among infants and young children. In 2007, WHO recommended the vaccine to be incorporated into national childhood immunisation programmes in every country [1]. In 2009, two pneumococcal vaccines with extended serotype coverage, 10-valent (PCV-10) and 13-valent (PCV-13), were introduced, and since then, they have been gradually replacing PCV-7 [2]. The PCV-10 conjugates to non-typable Haemophilus influenza carrier protein, while PCV-13 conjugates to the same carrier protein (CRM197) as PCV-7. In order to support the adoption of PCV-10 or PCV-13, cost-effectiveness studies have been performed in various countries. In general, results of these studies have demonstrated that the use of PCV-10 or PCV-13 is cost-effective or cost saving compared to PCV-7 vaccination programme in prevention of the disease caused by Streptococcus pneumoniae (S. pneumoniae) [3-6].

In Japan, PCV-7 was approved on October 26, 2009. The government disbursed a budget to encourage municipalities in launching a public 3+1 dose vaccination programme (3 primary doses and 1 booster dose) on November 26, 2010, which will continue until March 31, 2013. Therefore, currently all municipalities give subsidies to PCV-7 vaccinees. The attainable vaccination rate for Japanese

infants is considered to be about 60%, according to the ''Provisional Special Fund for the Urgent Promotion of Vaccination against Such Diseases as Cervical Cancer'' by the government in 2011. A study group of ten health institutions and affiliated paediatricians have reported that there was a decrease in invasive pneumococcal diseases (from 333 cases in 2010 to 113 cases in 2011) after the introduction of PCV-7 [7]. As to PCV-10 and PCV-13, both are not yet available in Japan, while the latter is now under the process of approval and experts have expressed their expectations [8]. The possible availability of PCV-13 raises the need to evaluate effective ways in protecting the birth cohort from pneumococcal-related diseases in Japan.

It is said that there are five hurdles to overcome in the diffusion process of new health intervention: quality, safety, efficacy, cost-effectiveness and affordability [9]. In regards to the cost-effectiveness and affordability of PCV-7 vaccination programme, our recently published economic evaluation of using PCV-7 to the birth cohort in Japan suggests that if we adopt WHO's criterion that an intervention is 'cost-effective' if ICER (in QALY) is between 1 and 3 times of GDP per capita, then PCV-7 vaccination programme would be an efficient use of finite resources in healthcare from the societal perspective, regardless of the co-payment level [10]. Furthermore, the study shows that if full subsidy is provided for the vaccination programme, the level of budget impact is less than ¥11,000,000 (US$137,500; US$1 = ¥80, based on the average

exchange rate of 2012) for a municipality with 1,000 birth cohort in the 1st year, and 2nd to 5th year birth cohort proportional to the birth cohort population of estimated future population.

This study aims to investigate the cost-effectiveness of replacing the current 3+1 dose schedule of PCV-7 vaccination programme with 3+1 dose schedule of PCV-13 vaccination programme in Japan, foreseeing the possible replacement after the approval of PCV-13.   The results should deepen our understanding about the implications of preventing pneumococcus-caused diseases among infants and young children to healthcare financing and inform policy makers of Japan as well as in other developed countries.   Since PCV-10 is not even under the process of approval, it is not considered as an alternative in this study, however, if in such case, we may evaluate with appropriate comparator, either PCV-7, PCV-13, other PCV products [11], or all.

2. Method

We conduct a cost-effectiveness analysis with Markov modelling from the societal perspective.   The Markov model is from our previous study [10], while epidemiological data and resource use are updated.   Japanese data sources are reviewed together with international literature to parameterise the model.

2.1. Programmes and Markov model

We define two vaccination programmes: current PCV-7 programme and the

possible replacement, i.e., PCV-13 programme, with the same vaccination schedule

(3+1).   We assume that vaccination is fully subsidised for the uptake of 4 doses of

either PCV-7 or PCV-13.   The average vaccine uptake rate for both vaccination

programmes is set as 76.1%, which is the rate of DPT vaccination programme in 2010

[12].   This rate is adopted for two reasons: first, it has been a mere two years since

the introduction of PCV-7 in Japan, and no adequate data is yet available to estimate

its uptake rate; secondly, the vaccination schedule of DPT is similar to that of PCV-7

and PCV-13.   We also assume that among the vaccinees of first 3 doses, 13.8% will

uptake PCV-7/PCV-13 alone, while 23.1% will uptake simultaneously with Hib

vaccine, and 63.1% will uptake simultaneously with one other vaccine listed in the

national immunisation schedule [13].   In regards to the 4th dose, 40% will uptake

PCV-7/PCV-13 alone, and 60% will uptake simultaneously with one other listed

vaccine [13].

   We then consider about the municipality's decision in launching a 5-year

programme, which is assumed for reconsideration or redesigning of the programme, as

it is often employed in organising public health programmes in Japan [14].   The birth

cohorts of five years used in the model are from Population estimates of Japan [15].

Incremental cost-effectiveness ratios (ICERs) of PCV-13 programme to PCV-7

programme are calculated to determine the efficiency of the resource use.

The disease model of the health effects of pneumococcal vaccination includes the possibility of subsequent pneumococcal disease, such as: bacteraemia (including sepsis), meningitis, all-cause hospitalised pneumonia, acute otitis media (AOM, including simple and complex), sequelae after meningitis, and death from or other than the related diseases in the model (Fig. 1). A Markov cycle for each stage is set at 1 year. The time frame is 5 years after the entering of a birth cohort because the diseases caused by S. pneumoniae decrease significantly among children aged 5 years and over [16]. Life expectancy of survived patient with or without neurological sequelae is assumed as 53.9 years or to have a life expectancy of Japanese population, respectively [10]. Adverse effects associated with vaccination are not considered because those of PCV-13 are similar to those of PCV-7 [17-19].

2.2. Outcomes estimation

Outcomes in terms of years of life saved (YOLS) and quality adjusted life year (QALY) are estimated by assigning transition probabilities and utility weights from the literature to the Markov model.

2.3. Annual incidence rates and case fatality rates

Annual incidence rates of meningitis and of bacteraemia among children younger than 5 years old without vaccination are derived from a three-year (2007-2009) nationwide survey by Kamiya et al. [20]; of AOM are computed by the AOM episodes

by child [21], multiplied by the "proportion of clinically diagnosed AOM episodes due to pneumococcus (34.1%)" [22]; of hospitalised community acquired pneumonia (CAP) are from a retrospective study of 18 hospitals with paediatric wards in Chiba city, Japan [23]. Proportions of meningitis that resulted in hearing impairment or neurological sequelae are from Kamiya et al. [20] and Iwata et al. [24]. Case fatality rates of meningitis and of bacteraemia are also from Kamiya et al. [20]; of hospitalised pneumonia are estimated from Patient survey [25] and Vital statistics [26]. Deaths from causes other than the above diseases are also from the Vital statistics [26]. All these rates are shown in Table 1.

2.4. Vaccine effectiveness

2.4.1. Direct effect

The vaccine effectiveness (VEs) of PCV-7 against vaccine-serotype- IPD (including bacteraemia and meningitis), vaccine-serotype- AOM, and hosiptalised radiograph-comfirmed pneumonia among children under 2 years old are 80%, 54%, and 27%, respectively, based on the systematic review reported by the Cochrane Collaboration [27,28]. The VEs of PCV-13 are not available at the time of this study. Based on the immunogenicity data, we assume PCV-13 is as immunogenic as PCV-7 for common serotypes and has comparable levels of antibody for serotypes unique to PCV-13 [2, 18, 19]. Proportion of IDP episodes due to PCV-7/PCV-13 serotype is

assumed as 68.5%/80.9% [7]; of hospitalised community acquired pneumonia (CAP) episodes, 66.7%/81.0% [23]; of AOM episodes, 68,2%/86.0%, for 0 to <3 years old, and 48,5%/77.9% fir 3 to <5 years old [29].   The VEs against IPD and AOM are of specific vaccine serotypes only, therefore, they are multiplied by the proportion of relevant disease episodes due to PCV-7/PCV-13 serotypes to adjust to our disease model, while the VEs against hospitalised pneumonia are not of specific vaccine serotypes, and therefore there is no need to adjust.   For those aged over 2 and under 5 years, the VEs against IPD and hospitalised pneumonia are assumed to decline by 3% annually for both PCV-7 and PCV-13 [30].   All these data are shown in Table 1.

No efficacy data against otitis media were available for serotypes 1, 3, 5, 6A, 7F, and 19A from the package insert of Prevenar 13® (brand name of PCV-13) sold in the US [31].   Therefore, we set two base-cases for analyses: "Base-case A", which assumes that the prevention of AOM by PCV-13 is limited to the seven serotypes of PCV-7 only; and "Base-case B", which assumes that the prevention of AOM by PCV-13 is straightforwardly extended to cover non-PCV-7 serotypes.

2.4.2. Indirect effects

We do not consider the net indirect vaccine effect (herd protection minus serotype replacement effect) in our base-case analysis, but conduct four scenario analyses by assuming different net indirect effects among children aged under 5 years

old as observed in European countries and the US. Assumptions made for each

scenario and two base-cases are shown in Table 2. The net indirect effect in

non-vaccinated children older than 5 years old is not considered in the scenario

analyses because of the discrepancies among reports from previous studies [32]. In

the US, indirect effects was observed among adults after the nationwide

implementation of PCV-7 in 2000, while in European countres, such as Spain, France,

and the UK, no overall reduction of IPD incidences were observed among adults even

after three years of introduction in routine vaccination [32]. Rozenbaum indicates

that possible factors responsible for these differences may include the

vaccine-serotype coverage, and/or implemented vaccination schedules, and/or

antibiotic resistance rates, and/or pneumococcal disease incidences prior to

vaccination.

2.5. Costing

From the societal perspective, costing should cover the opportunity costs borne

by various economic entities in the society [33]. In the context of this study, the

amount of direct payments costs borne by municipal authorities, vaccinees, patients and

social insurers are considered, while indirect costs of vaccination programme are not

included, because it is assumed that the programme is built within the public health

services infrastructure. Therefore, costs of vaccination, treatment costs of

pneumococcal-related diseases and costs associated to care-giver's lost productivity, such as accompanying a child for vaccination, for medical treatment, or to take care of a child with sequelae, are counted. Productivity loss due to mortality or morbidity is not included, as including this into cost-effectiveness analysis may be argued as double counting while survived cases are incorporated in the utility weights and disease duration in calculating QALYs [33].

2.5.1. Direct medical costs

The vaccination cost per a shot of PCV-7 is assumed at ¥10,000 (US$125) [10]; per a shot of PCV-13 is assumed at 1.3 times that of PCV-7 based on the report from "The Pharma Letter" [34]. Treatment costs per episode of survived/fatal bacteraemia, survived/fatal meningitis, and long-term treatment costs for an individual with hearing impairment or neurological sequelae are according to Iwata et al. [24]. Treatment costs per episode of pneumonia caused by S. pneumoniae are according to Ishiwada et al. [35]. Treatment costs per episode of AOM are the weighted average of simple and complex cases reported by Yamanaka et al. [21]. The proportions of complex cases are: 37%, 49%, 25%, 19%, and 14%, for children aged 0 to <1, 1 to <2, 2 to <3, 3 to <4, and 4 to <5, respectively [21]. All these costs are shown in Table 3.

2.5.2. Productivity loss by care-giver

Under the context of this study, productivity loss per disease episode or per shot

is valued as a product of care-giver's absent working hours from paid employment (8 working hours/day) and an average hourly wage, ¥1,328 (US$17), of Japanese women labourers [36]. Productivity loss of a care-giver to accompany a child for one uptake of vaccine is assumed as a half of a day (4h) when uptaking PCV-7 or PCV-13 alone, $1/2 \times 4h$ when uptaking simultaneously with Hib vaccine. $1/2 \times 4h$ is assumed because Hib vaccination programme was introduced on the same day as PCV-7 vaccination programme in Japan, and therefore, 4h of productivity loss should be shared equally in simultaneous uptake of PCV-7/PCV-13 and Hib vaccine. And 0h, when uptaking simultaneously with one other listed vaccine, because it can be assumed that no incremental productivity loss occurs to uptake PCV-7/PCV13 in particular. As to the productivity loss per disease episode, the frequency of outpatient visits and the number of hospitalisation days of a meningitis episode are from Yamanaka et al. [21]; of a pneumonia episode are from Ishiwada [35]. We assume 4 absent working hours for one outpatient visit and 8 absent working hours for one hospitalised day. The average absent working hours of an AOM episode are the weighted average of simple and complex AOM derived from Yamanaka et al. [21]. We assume that the absent working hours of a care-giver to take care of one child with hearing impairment or neurological sequelae is 8 hours per day until the child is admitted to special support education system, which is at age 6 in Japan.

2.6. Discounting

Costs and outcomes were discounted at a rate of 3% [33].

2.7. Scenario analyses, sensitivity analyses, and probabilistic analyses

In order to assess the impact of herd effects on outcomes of PCV-7/PCV-13 vaccination, scenario analyses, which assume four different net indirect effects in non-vaccinated children aged under 5 years old (Table 2), are performed: Scenario-1 limits the herd effect to IPD only; Scenario-2 extends the effect to IPD and hospitalised pneumonia; Scenario-3 extends the effect to IPD and AOM; and Scenario-4 assumes the effect to all the diseases, i.e., IPD, hospitalised pneumonia and AOM. We assume the protection resulted from herd effects would be as effective as direct effects of vaccination, based on the report from the US [37]. One-way sensitivity analyses are performed on cost of one shot of PCV-13 as well as on the VEs of PCV-7 and PCV-13, which several studies have reported to have a significant impact on the results. For a cost of one shot of PCV-13, lower and upper values are set at ¥10,000 (US$125, equal to the current cost of PCV-7) and ¥20,000 (US$250, double the current cost of PCV-7), respectively. For the VEs of PCV-7, the lower value is changed by -20%, while the upper value is set equal to the VEs of PCV-13. On the other hand, for the VEs of PCV-13, the upper value is changed by +20%, and the lower value is set equal to the VEs of PVC-7. Sensitivity analyses on epidemiological data, life expectancy, utility

weights and treatment costs of disease episodes are omitted because these are assumed as similar in both PCV vaccination programmes.

We also conduct a thousand times Monte Carlo simulation, i.e., probabilistic analyses, for which VEs are assumed to have an equilateral triangle distribution corresponding to the range tested in one way sensitivity analyses. Other variables are fixed at their base-case values.

3. Results

3.1. Avoided cases

The estimated disease cases avoided by PCV-7/PCV-13 vaccination programme compared with no programme for 100,000 birth cohort in the five year period are as follow: 8.2/9.7 cases of meningitis, 49.4/58.4 cases of bacteraemia, 1739.4/ 2112.9 cases of hospitalised pneumonia, 66,188/66,188 (Base-case A) or 72,728 (Base-case B) of AOM, and 1.86/2.26 cases of death due to either meningitis, bacteraemia or pneumonia. If PCV-13 replaces PCV-7, the estimated incremental number of avoided cases will be: 1.49 of meningitis, 8.94 of bacteraemia, 373.5 of hospitalised pneumonia, none or 6540.2 of AOM in Base-case A or Base-case B, respectively, and 0.40 cases of death due to either meningitis, bacteraemia or pneumonia. The reduced disease cases resulting from replacing PCV-7 with PCV-13 would be 18.1%, 21.5%, and 9.9%, for IPD, hospitalised pneumonia, and AOM, respectively.

3.2. Cost, effectiveness, and cost-effectiveness

Given the purpose of this study, the description should focus on the comparison between PCV-13 programme and PCV-7 programme. The results of the comparison between PCV-7/PCV-13 against no-programme are shown in Table 4 as reference.

Table 4 shows the results of base-case analyses. When comparing PCV-13 programme with PCV-7 programme, estimated average incremental effects per child are 0.0002QALY/0.0001YOLS for Base-case A, and 0.0011QALY/0.0001YOLS for Base-case B. In terms of QALY gained, IPD contributed 7.1%, hospitalised pneumonia contributed 11.9%, and AOM contributed 81.0% to the figures (in Base-case B).

PCV-13 programme reduces both disease treatment costs and care-giver's productivity loss due to disease treatment. However, when the care-giver's productivity loss is not included, the reduced disease treatment costs alone do not offset the vaccination cost, which means that the vaccination programme turns out to be 'gain more but cost more'. Estimated ICERs are ¥37,722,901 (US$471,536) per QALY gained or ¥5,4261,241 (US$678,266) per YOLS gained for Base-case A; ¥343,830 (US$4,298) per QALY gained or ¥2,606,959 (US$32,587) per YOLS gained for Base-case B. When the care-giver's productivity loss is included, the ICERs are ¥35,584,455 (US$444,806) per QALY gain or ¥51,185,265 (US$639,816) per YOLS gain for base-case A. While for Base-case B, the sum of reduced disease treatment

costs and reduced caregiver's productivity loss outweighs the vaccination cost. It can

be concluded that PCV-13 programme not only gains more QALY/YOLS but also saves

money compared to PCV-7 programme.

3.3. Uncertainty analyses

Table 5 shows the results of eight scenario analyses. ICER decreases as

expected from indirect effect. In Base-case A, it decreases from ¥37,722,901

(US$471,536) to ¥33,661,992 (US$420,775) in Scenario-1; to ¥27,824,591

(US$347,807) in Scenario-2; to ¥31,387,702 (US$392,346) in Scenario-3; and to

¥25,682,885 (US$321,036) in Scenario-4; per QALY, when care-giver's productivity

loss is not included. In Base-case B, it decreases from ¥343,830,(US$4,298) to

¥308,676 (US$3,858) in Scenario-1; to ¥115,860 (US$1,448) in Scenario-2; cost less

and gain more in both Scenario-3 and Scenario-4; per QALY, when caregiver's

productivity loss is not included. It consistently costs less and gains more in all eight

scenarios when caregiver's productivity loss is included.

Fig. 2(a) and 2(b) show how the ICER of PCV-13 programme varies with

changing costs per shot compared to PCV-7 programme. PCV-13 dominates (costs

less and gains more) PCV-7 at cost per shot equal to or lower than that of PCV-7, i.e.,

¥10,000 (US$125) in Base-case A regardless of care-giver's productivity loss, and

regardless of measuring QALY or YOLS; While in Base-case B, ¥12,000 (US$150) or

¥16,000 (US$200), when care-giver's productivity loss is included or not included, respectively.

Fig.3 shows the results of one-way sensitivity analyses performed on VEs which decrease or increase the ICER more than ¥500,000 (US$6,250) per QALY. The top 10 variables are all related to VE against AOM. Among the variables, the VE of PCV-13 against AOM (1 to 2 years old) shows the largest impact on the result. The upper/lower value of this variable decrease/increase the ICER by ¥894,798 (US$11,185)/¥887,925 (US$11,099) per QALY, which is -260%/+258% of the ICER of the base-case.

Fig. 4 presents four cost-effectiveness acceptability curves (CEACs) estimated by the probabilistic sensitivity analyses: For Base-case A, when productivity loss is included/not included, the probability of ICER to be less than ¥5,000,000 (US$62,500) per QALY is 3.8%/0.1%, respectively. For Base-case B, when productivity loss is included/not included, the probability that PCV-13 programme dominates PCV-7 programme is 99.0%/42.5%, and the probability of ICER to be less than ¥5,000,000 (US$62,500) per QALY is 99.9%/95.0%.

4. Discussion

We estimate the cost-effectiveness of replacing the current PCV-7 vaccination

programme with PCV-13 vaccination programme, and the effectiveness of PCV-13 is calculated based on the effects of PCV-7 and the serotype coverage of PCV-13 compared to PCV-7, as done in other studies [4- 6].

Our base-case analyses, which sets the cost of PCV-13 per shot at 1.3 times that of PCV-7 (¥13,000/US$163), shows that in Base-case A (assumed PCV-13 has no additional protection against AOM compared to PCV-7), replacing PCV-7 with PCV-13 will cost an additional ¥37,722,901 (US$471,536) or ¥35,584,455 (US$444,850) per additional QALY when the caregiver's productivity loss is not included or is included, respectively.   While in Base-case B (assumed PCV-13 has additional protection against AOM compared to PCV-7), ¥343830 (US$4,298) per additional QALY or more QALY is gained by saving money without or with caregiver's productivity loss, respectively.

Sensitivity analyses on cost of one shot of PCV-13 show that in Base-case A, if the cost of one shot of PCV-13 is equal to that of PCV-7, i.e., ¥10,000 (US$125), replacing PCV-7 with PCV-13 will save money and gain more QALY or YOLS regardless of caregiver's productivity loss.   At cost equal to or less than 11,000 (US$138), ICER will be lower than ¥10 million (US$125,000) per QALY regardless of caregiver's productivity loss.   While in Base-case B, at ¥12,000 (US$150)/¥16,000 (US$200) per shot, the replacement will save money and gain more QALY or YOLS regardless of caregiver's productivity loss.

Sensitivity analyses on VEs performed on Base-case B show that the VE of PCV-13 against AOM (1 to <2 year) has the largest impact on the result, with its lower/upper value increasing/decreasing the ICER about ¥9,000,000 (US$11,250) per QALY.

The probabilistic sensitivity analyses show that the probabilities of PCV-13 programme to be under ¥5,000,000 (US$62,500) per QALY are 0.1% (Base-case A, care-giver's productivity loss not included) to 99.9% (Base-case B, care-giver's productivity loss included).

In Base-case B, the ICERs in QALY of our base-case analyses, scenario analyses and sensitivity analyses are all less than a willingness-to-pay threshold suggested for healthcare intervention, i.e., ¥5,000,000 (US$62,500) per QALY gained [34], and are under WHO's cost-effective criterion for intervention, i.e., less than 3 times of GDP per capita (≑¥11,000,000 or US$137,500 in Japan) [39].   Therefore, when we consider the "value for money", the replacement of PCV-7 with PCV-13 vaccination programme would be a socially acceptable option in Japan from the viewpoint of health economics. On the other hand, in Base-case A, unless the cost of one PCV-13 shot is equal to or less than ¥11,000 (US$138), the ICERs would all be over ¥11,000,000 (US$137,500). Therefore the replacement is not considered a socially acceptable option in Japan.

A recent study reported the cost-effectiveness ratio (CER) of Rotavirus

vaccination programme in Japan, of which ratio was ¥9.8 million per QALY.[40]   This

is larger than our CERs of PCV-7 or PCV-13, which is ¥6.4 million or ¥9.0 million per

QALY, respectively.   Several studies from overseas reported on the cost-effectiveness

of introducing PCV-13.   Among them, some compared PCV-7 and PCV-13 with

no-programme from the societal perspective and found PCV-13 is more cost-effective

than PCV-7 with or without considering net-indirect effect [6, 32].   By taking the

cost-effective ratios (CERs) of PCV-7/PCV-13 vaccination programme and comparing

them to that of no-programme, our study yields a result that is consistent with those

previous studies.   On the other hand, some studies evaluated the transition of PCV-7 to

PCV-13 [3-5, 41].   Conclusions drawn from the replacement of PCV-7 with PCV-13

ranged from borderline cost-effective (England) [41] to cost-saving (USA, Germany,

Greece, and The Netherlands) [3-5].   Although there are lots of differences between

our study and theirs, we share the same determination in evaluating the replacement of

PCV-7 to PCV-13, as it is highly relevant to countries where PCV-7 has been offered

under the national immunisation programme.

Our analysis is simple and straightforward based on the limited knowledge of

epidemiology, and the assumption we made on efficacy or effectiveness of PCV-7 and

PCV-13 may suggest an overestimation or underestimation of the results.   However,

evidences adopted are the best available ones to date, and assumptions made are the

most conservative under the current uncertainty.   The main limitations of our study are as follows: First, clinical evidences which show the effectiveness of vaccination in reducing annual incidence rates of the diseases in our model are adopted from studies carried out in other countries, since no similar study has been done in Japan.   There should be differences in ethnicity as well as in the health system between those countries and Japan.   Second, annual incidence rate of hospitalised pneumonia used in this study is based on a study done in only one prefecture because of the unavailability of national surveillance data, and such data would have a bias.   Third, we did not include the benefits of vaccination in preventing antibiotic resistance in our model. Including this benefit would bring more cost-effective results given that the serotypes identified as penicillin resistant and covered by PCV-7 is above 80% in Japan [8, 29].

5. Conclusion

Our study finds that if PCV-13 had additional protection against AOM compared to PCV-7 and cost per PCV-13 shot is 1.7 times less than that of PCV-7, a PCV-13 vaccination programme offered to the birth cohort in Japan is likely to be a socially acceptable option compared to the current PCV-7 vaccination programme. Furthermore, if cost per PCV-13 shot is 1.2 times less than that of PCV-7, replacing PCV-7 with PCV-13 will save money and gain more QALYs.   However, if PCV-13 had no additional protection against AOM, the replacement can only be acceptable if cost

per PCV-13 shot is 1.1 times less than of that of PCV-7.   Due caution is needed in

transferring these findings from our Japanese model to other health system, even so,

replacing PCV-7 with PCV-13 to protect the birth cohort could be economically

acceptable in developed countries.

Acknowledgements

References

1. Pneumococcal conjugate vaccine for childhood immunization–WHO position paper. Wkly Epidemiol Rec 2007;82(12):93–104.

2. WHO position paper on pneumococcal vaccines-2012. Wkly Epidemiol Rec 2012;(87)14:129–144. http://www.who.int/wer

3. Blank PR, Szucs TD. Cost-effectiveness of 13-valent pneumococcal conjugate vaccine in Switzerland. Vaccine 2012;30(28):4267-75.

4. Strutton DR, Farkouh RA, Earnshaw SR, Hwang S, Theidel U, Kontodimas S, et al. Cost-effectiveness of 13-valent pneumococcal conjugate vaccine: Germany, Greece, and The Netherlands. J Infect 2012;64(1):54-67.

5. Rubin JL, McGarry LJ, Strutton DR, Klugman KP, Pelton SI, Gilmore KE, et al. Public health and economic impact of the 13-valent pneumococcal conjugate vaccine (PCV13) in the United States. Vaccine 2010;28(48):7634-43.

6. Tyo KR, Rosen MM, Zeng W, Yap M, Pwee KH, Ang LW, et al. Cost-effectiveness of conjugate pneumococcal vaccination in Singapore: Comparing estimates for 7-valent, 10-valent, and 13-valent vaccines. Vaccine 2011;29(38):6686-94.

7. Morozumi M, Chiba N, Okada T, Sakata H, Matsubara K, Iwata S, et al. Antibiotic susceptibility in relation to genotype of Streptococcus pneumoniae, Haemophilus influenzae, and Mycoplasma pneumoniae responsible for

community-acquired pneumonia in children. J Infect Chemother. 2012 Oct 30. [Epub ahead of print]

8. Chiba N, Morizumi M, Sunaoshi K, Takahashi S, Sunakawa K, Ubukata K, et al. Serotype and antibiotic resistance of isolates from patients with invasive pneumococcal disease in Japan. Epidemiol Infect 2010;138:61-8.

9. Trueman P, Drummond M, Hutton J. Developing guidance for budget impact analysis. Pharmacoeconomics 2001;19:609-21.

10. Hoshi SL, Kondo M, Okubo I. Economic evaluation of vaccination programme of 7-valent pneumococcal conjugate vaccine to the birth cohort in Japan. Vaccine 2012;30(22):3320-8.

11. Skinner JM, Indrawati L, Cannon J, Blue J, Winters M, Macnair J, et al. Pre-clinical evaluation of a 15-valent pneumococcal conjugate vaccine (PCV15-CRM197) in an infant-rhesus monkey immunogenicity model. 2011; 29(48):8870-6.

12. Ministry of Health, Labour and Welfare. Report on health center activities and health services for the year 2010. Tokyo: Health and Welfare Statistics Association; 2011 [in Japanese].

13. Pfizer Japan Inc. Prevenar®: marketing brochure. Tokyo: Pfizer Japan Inc.; 2012 [in Japanese].

14. Preventive Vaccination Law, Supplementary Provisions, Extract, Pub. L. No. 116,

Article 2; November 7, 2001.

15. Ministry of Internal Affairs and Communications. Population estimates of Japan. Tokyo: Statistics Bureau; 2002.

16. Sakata H, Shirai M, Kaijino M, Takase M, Okamoto T, Niura N, et al. Epidemiological study of bacterial meningitis in children in Kamikawa subprefecture in Hokkaido between 1988 and 2002. Acta Paediatr Jpn 2004;108:401–5 [in Japanese].

17. Ministry of Health, Labour and Welfare. Syoniyo haien kyukin wakutin, bihu wakutin no anzensei no hyouka kekka ni tuite. Press release 2011, March 24 [in Japanese].

18. Kieninger DM, Kueper K, Steul K, Juergens C, Ahlers N, Baker S, et al. Safety, tolerability, and immunologic noninferiority of a 13-valent pneumococcal conjugate vaccine compared to a 7-valent pneumococcal conjugate vaccine given with routine pediatric vaccinations in Germany. Vaccine 2010;28(25):4192-203.

19. Esposito S, Tansey S, Thompson A, Razmpour A, Liang J, Jones TR, et al. Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine compared to those of a 7-valent pneumococcal conjugate vaccine given as a three-dose series with routine vaccines in healthy infants and toddlers. Clin Vaccine Immunol 2010; 17(6):1017–26.

20. Kamiya H. Wakutin no yuyousei koujou no tame no ebidensu oyobi housaku ni kansuru kenkyu. Heisei 19 nendo-21 nendo sogo kenkyu hokokusho. Report of Health and Labour Sciences Research Grants. Tokyo: Ministry of Health, Labour, and Welfare; 2010 [in Japanese].

21. Yamanaka N, Hotomi M, Sugita R. Cost-effectiveness of pneumococcal conjugate vaccine in Japan: Estimation on acute pneumococcal otitis media in children. Japanese Journal of Pediatrics 2008;61:2221–32 [in Japanese].

22. Suzuki K, Kurono Y, Kobayashi T, Nishimura T, Baba S, Harabuchi Y, et al. The fourth nationwide survey of clinical isolates from patients with otolaryngological field infections. J Jpn Soc Infect Dis Otolaryngol 2008;26:15–26 [in Japanese].

23. Takana J, Ishiwada N, Wada A, Chang B, Hishiki H, Kurosaki T, et al. Incidence of childhood pneumonia and serotype and sequence-type distribution in Streptococcus pneumonia isolates in Japan. Epidemiol Infect 2012;140(6):1111-21.

24. Iwata S, Ishiwada N, Sakata H, Sakano T, Sato Y, Nakano T, et al. Burden of illness of bacterial meningitis and bacteremia caused by Streptococcus pneumonia in children. Japanese Journal of Pediatrics 2008;61:2206-20 [in Japanese].

25. Social Statistics Division, Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. Heisei 20 nen kanja chosa. Tokyo: Ministry of Health, Labour and Welfare; 2008 [in Japanese].

26. Ministry of Health, Labour and Welfare. Vital statistics of Japan 2006. Tokyo: Health and Welfare Statistics Association; 2008 [in Japanese].

27. Lucero MG, Dulalia VE, Nillos LT, Williams G, Parreño RAN, Nohynek H, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. Cochrane Database of Systematic Reviews 2009; Issue 4. Art. No.: CD004977. DOI: 10.1002/14651858.CD004977.pub2.

28. Jansen AGSC, Hak E, Veenhoven RH, Damoiseaux RAMJ, Schilder AGM, Sanders EAM. Pneumococcal conjugate vaccines for preventing otitis media. Cochrane database of Systematic Reviews 2009; Issue 2, Art. No.:CD001480. DOI:10.1002/14651858.CD001480.pub3.

29. Hotomi M, Billal DS, Kamide Y, Kanesada K, Uno Y, Kudo F, et al. Serotype distribution and penicillin resistance of Streptococcus pneumoniae isolates from middle ear fluids of pediatric patients with acute otitis media in Japan. Clin Microbiol 2008;46:3808–10.

30. Hsu HE, Shutt KA, Moore MR, Beall BW, Bennett NM, Craig AS, et al. Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. N Engl J Med 2009;360(3):244-56.

31. Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197

Protein)) [Package insert]. Philadelphia, USA: Wyeth Pharmaceuticals, Inc.; 2010.

32. Rozenbaum MH, Boersma C, Postma MJ, Hak. Observed differences in invasive pneumococcal disease epidemiology after routine infant vaccination. Expert Rev Vaccines. 2011 Feb;10(2):187-99.

33. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for Economic Evaluation of Health Care Programmes. 3rd ed. Oxford University Press, Oxford, 2004.

34. The Pharma Letter. Pfizer gets US FDA approval for Prevnar 13, a Wyeth drug with blockbuster sales outlook. 25 February 2010, London, UK. http://www.thepharmaletter.com/file/52409/pfizer-gets-us-fda-approval-for-prevnar -13-a-wyeth-drug-with-blockbuster-sales-outlook.html (Sep 23, 2012).

35. Ishiwada N, Iwata S, Sakata H, Sakano T, Sato Y, Nakano T, et al. Burden of illness of pneumonia caused by Streptococcus pneumoniae in children. Japanese Journal of Pediatrics 2008;61:2194–204 [in Japanese].

36. Ministry of Health, Labour and Welfare. Basic Survey on Wage Structure 2009. Tokyo: Health and Welfare Statistics Association; 2010 [in Japanese].

37. Ray GT, Pelton SI, Klugman KP, Strutton DR, Moore MR. Cost-effectiveness of pneumococcal conjugate vaccine: an update after 7 years of use in the United States. Vaccine. 2009;5;27(47):6483-94.

38. 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.

39. World Health Organization. WHO guide for standardization of economic evaluations of immunization programmes. WHO Document Production Services: Geneva, Switzerland; 2008.

40. Sato T, Nakagomi T, Nakagomi O. Cost-effectiveness analysis of a universal rotavirus immunization program in Japan. Jpn J Infect Dis. 2011;64(4):277-83.

41. van Hoek AJ, Choi YH, Trotter C, Miller E, Jit M. The cost-effectiveness of a 13-valent pneumococcal conjugate vaccination for infants in England. Vaccine. 2012;26;30(50):7205-13.

Table 1. Epidemiological data used on model

Variable						Reference
Vaccine uptake rate	76.1%					12
Population of birth cohort entering the model, unit:1000	Total	Male	Female			15
1st year	1,004	515	489			
2nd year	981	504	478			
3rd year	954	489	464			
4th year	926	475	451			
5th year	900	462	438			
	Age groups					
	0 to <1	1 to <2	2 to <3	3 to <4	4 to <5	
Annual incidence rates per 100,000 population						
Invasive pneumococcal disease cases: meningitis	7.46	3.83	1.11	0.94	0.27	20
Invasive pneumococcal disease cases: bacteraemia	15.2	45.4	12	5.8	4	20
Clinically diagnosed AOM episodes	103,100	113,881	67,160	52,589	40,371	21
All-causes hospitalised CAP	1,760	1,760	1,760	1,760	1,760	23
Proportion of meningitis that results to hearing impairment; %	3.3	3.3	3.3	3.4	3.4	20,24
Proportion of meningitis that results to neurological sequelae; %	15.7	15.7	15.7	15.6	15.6	20,24
Proportion of clinically diagnosed AOM episodes due to pneumococcus; %	34.1	34.1	34.1	34.1	34.1	22
Case fatality rate; %						
Bacteraemia	0.04	0.04	0.04	0.04	0.04	20
Meningitis	0.21	0.21	0.21	0.21	0.21	20
Hospitalised pneumonia	0.11	0.11	0.11	0.11	0.11	25,26
Vaccine effectiveness (VE) of PCV-7*; %						
In reducing vaccine serotype IPD	80.0	80.0	77.6	75.3	73.0	27
In reducing vaccine serotype AOM	54.0	54.0	572.4	50.8	49.3	27
In reducing hospitalised pneumonia	27.0	27.0	26.2	25.4	24.6	28
Proportion of IPD episodes due to PCV-7 serotype; %	68.5					7
Proportion of IPD episodes due to PCV-13 serotype; %	80.9					7
Proportion of hospitalized CAP episodes due to PCV-7 serotype; %	66.7					23
Proportion of hospitalized CAP episodes due to PCV-13 serotype; %	81.0					23
Proportion of AOM episodes due to PCV-7 serotype; %	68.2	68.2	68.2	48.5	48.5	29
Proportion of AOM episodes due to PCV-13 serotype; %	86.0	86.0	86.0	77.9	77.9	29
Life expectancy of neurological sequelae	53.9					10
Life expectancy of Japanese population at age 5	74.9 male; 80.8 female					10
Utility weight						10
Healthy	1					
Hearing impairment	0.9					

Neurological sequelae	0.57
Curable bacteraemia	0.9921
Curable meningitis	0.9768
Curable pneumonia	0.994
AOM	0.995
Death	0

*VEs of PCV-13 are assumed to be as immunogenic as PCV-7 for common serotypes and has comparable levels of antibody for serotypes unique to PCV-13.

Table 2 Base-cases and scenarios

Base-case A	No net indirect effect. Not effective against serotypes unique to PCV-13 (1, 3, 5, 6A, 7F, 19A)
Base-case B	No net indirect effect. Effective against serotypes unique to PCV-13 (1, 3, 5, 6A, 7F, 19A)
Scenario-1	Net indirect effect to non-vaccinated aged under 5. The effect to IPD only. No net indirect effect to aged over 5.
Scenario-2	Net indirect effect to non-vaccinated aged under 5. The effect to IPD, hospitalised pneumonia. No net indirect effect to aged over 5.
Scenario-3	Net indirect effect to non-vaccinated aged under 5. The effect to IPD, AOM. No net indirect effect to aged over 5.
Scenario-4	Net indirect effect to non-vaccinated aged under 5. The effect to IPD, hospitalised pneumonia, AOM. No net indirect effect to aged over 5.

Table 3 Costs

Variable						Reference
Cost per PCV-7	¥10,000					10
Cost per PCV-13	¥13,000					34
	Age groups					
Treatment cost:	0 to <1	1 to <2	2 to <3	3 to <4	4 to <5	
Bacteraemia episode, survive	¥419,153	¥419,153	¥419,153	¥392,802	¥392,802	24
Bacteraemia episode, death	¥1,032,126	¥1,032,126	¥1,032,126	¥1,010,205	¥1,010,205	24
Meningitis episode, survive	¥852,642	¥852,642	¥852,642	¥843,867	¥843,867	24
Meningitis episode, death	¥1,470,421	¥1,470,421	¥1,479,196	¥1,510,669	¥1,510,669	24
Pneumonia episode	¥221,133	¥221,133	¥221,133	¥164,916	¥164,916	35
AOM episode	¥31,990	¥35,313	¥61,927	¥43,659	¥44,359	21
Hearing impairment (long term treatment)/year	¥79,422	¥79,422	¥79,422	¥78,057	¥78,057	21
Neurological sequelae (long term treatment)/year	¥420,464	¥420,464	¥420,464	¥380,671	¥380,671	21
Variables related to care-giver's productivity loss	Age groups					
Frequency of outpatient visits/number of hospitalisation days	0 to <1	1 to <2	2 to <3	3 to <4	4 to <5	
Bacteraemia episode		2.9 visits/11.5 days		2.8 visits/10.5 days		21
Meningitis episode		8.1 visits/22.7 days		7.8 visits/21.1days		21
Pneumonia episode		2.7 visits/6.8 days		2.8 visits/4.9 days		35
Hearing impairment						21
Neurological sequelae	8 hours per day until the child is admitted to special support education system					21
Absent working hours per AOM episode (h)	33.6	27.7	50.3	43.1	39.4	
Average hourly wage of Japnaese women labourers	¥1,328					36

US$1 = ¥80

Table 4 Results of Base-case analyses

	Base-case A: PCV-13 with no additional VE to PCV-7 on AOM*				Base-case B: PCV-13 with additional VE to PCV-7 on AOM			
	Cost per child				Cost per child			
	Vaccine cost	Diseases treatment costs	Productivity loss (uptake vaccine)	Productivity loss (disease treatment)	Vaccine cost	Diseases treatment costs	Productivity loss (uptake vaccine)	Productivity loss (disease treatment)
No programme	¥0	¥64,346	¥0	¥62,931	¥0	¥64,346	¥0	¥62,931
PCV-7	¥28,725	¥49,747	¥4,414	¥47,924	¥28,725	¥49,747	¥4,414	¥47,924
PCV-13	¥37,342	¥48,975	¥4,414	¥47,479	¥37,342	¥41,507	¥4,414	¥38,646
	Effect per child				Effect per child			
	QALY	YOLS			QALY	YOLS		
No progaramme	32.8087	32.8152			32.8087	32.8152		
PCV-7	32.8109	32.8158			32.8109	32.8158		
PCV-13	32.8111	32.8160			32.8120	32.8160		
	Cost/QALY	Cost/QALY	Cost/YOLS	Cost/YOLS	Cost/QALY	Cost/QALY	Cost/YOLS	Cost/YOLS
CER/ICER	Without productivity loss	With productivity loss	Without productivity loss	With productivity loss	Without productivity loss	With productivity loss	Without productivity loss	With productivity loss
PCV-7 vs. No programme	¥6,352,110	¥1,588,575	¥23,512,220	¥5,880,083	¥6,352,110	¥1,588,575	¥23,512,220	¥5,880,083
PCV-13 vs. No programme	¥9,034,940	¥4,495,903	¥29,476,620	¥14,667,948	¥4,368,278	cost less, gain more	¥19,457,218	cost less, gain more
PCV-13 vs. PCV-7	¥37,722,901	¥35,584,455	¥54,261,241	¥51,185,265	¥343,830	cost less, gain more	¥2,606,959	cost less, gain more

*Based on the package insert of Prevenar®

Table 5 Results of Scenario analyses

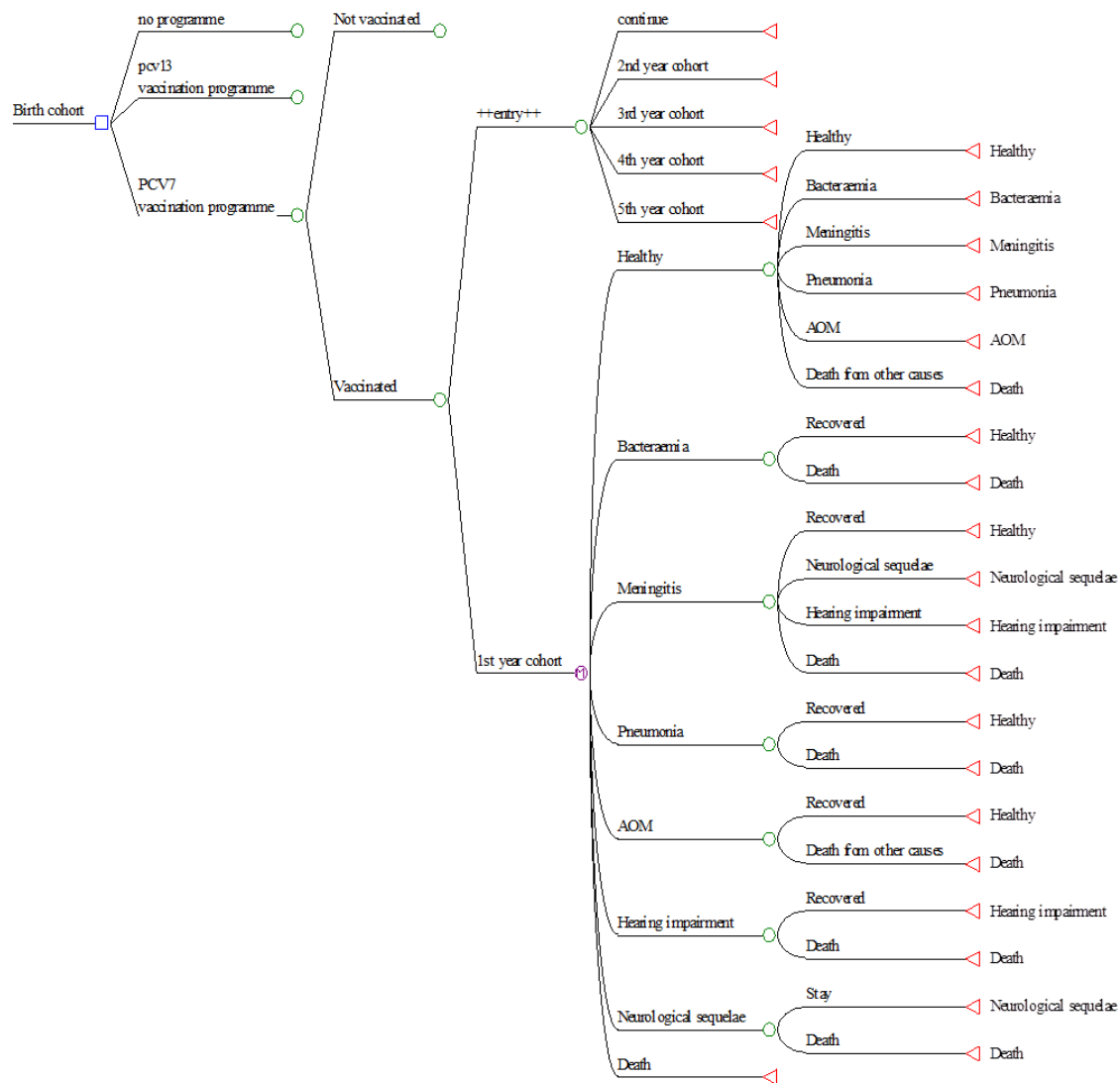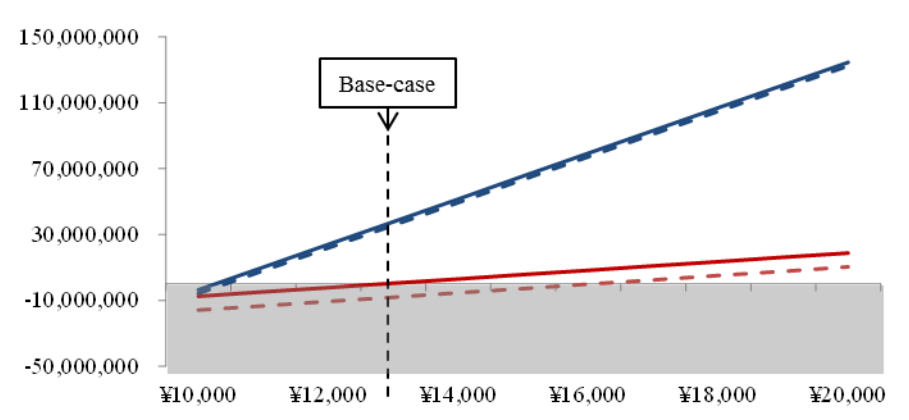| | PCV-13 vs. PCV7 | |
| | Cost/QALY | Cost/QALY |
	Without productivity loss	with productivity loss
Base-case A	¥37,722,901	¥35,584,455
Scenario-1	¥33,661,992	¥31,387,802
Scenario-2	¥27,824,591	¥25,683,001
Scenario-3	¥31,387,702	¥31,387,802
Scenario-4	¥25,682,885	¥25,683,001
Base-case B	¥343,830	cost less, gain more
Scenario-1	¥308,676	cost less, gain more
Scenario-2	¥115,860	cost less, gain more
Scenario-3	cost less, gain more	cost less, gain more
Scenario-4	cost less, gain more	cost less, gain more

continue

no programme — Not vaccinated

pcv13 vaccination programme

2nd year cohort

3rd year cohort

++entry++

4th year cohort

Birth cohort

5th year cohort

PCV7 vaccination programme

Healthy — Healthy

Bacteraemia — Bacteraemia

Meningitis — Meningitis

Healthy — Pneumonia — Pneumonia

AOM — AOM

Death from other causes — Death

Vaccinated

Bacteraemia — Recovered — Healthy

Death — Death

Recovered — Healthy

Neurological sequelae — Neurological sequelae

Meningitis — Hearing impairment — Hearing impairment

Death — Death

1st year cohort

Pneumonia — Recovered — Healthy

Death — Death

AOM — Recovered — Healthy

Death from other causes — Death

Hearing impairment — Recovered — Hearing impairment

Death — Death

Neurological sequelae — Stay — Neurological sequelae

Death — Death

Death

Fig. 1 Markov model

1st to 5th year birth cohort are from Population estimates of Japan.

"Healthy" means being without the diseases defined by the model.   The "++entry++"indicates new birth cohort which falls into programmes during the 2nd to 5th year after the start of the vaccination programme. No program is shown as reference.
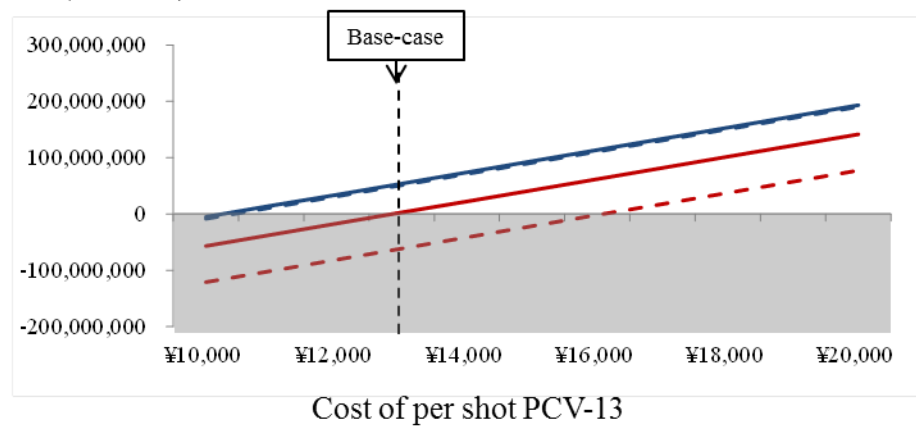
Fig. 2 The effect on ICERs by changing cost of PCV-13
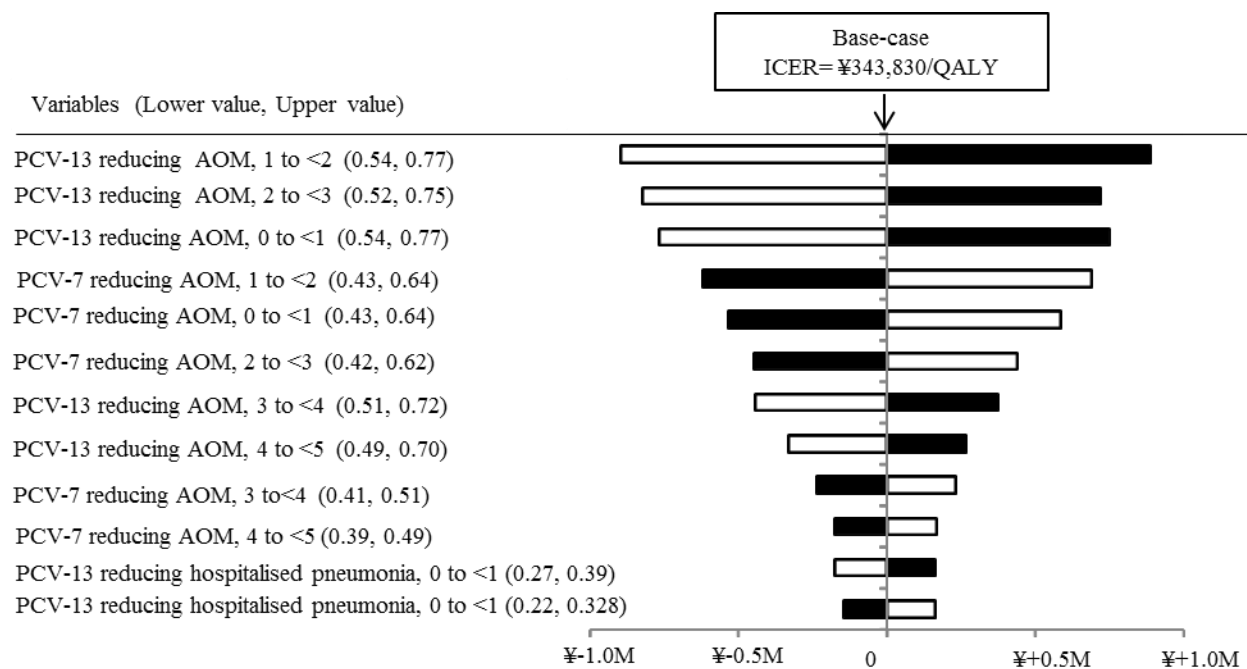The grey area shows cost saving, i.e., cost less and gain more

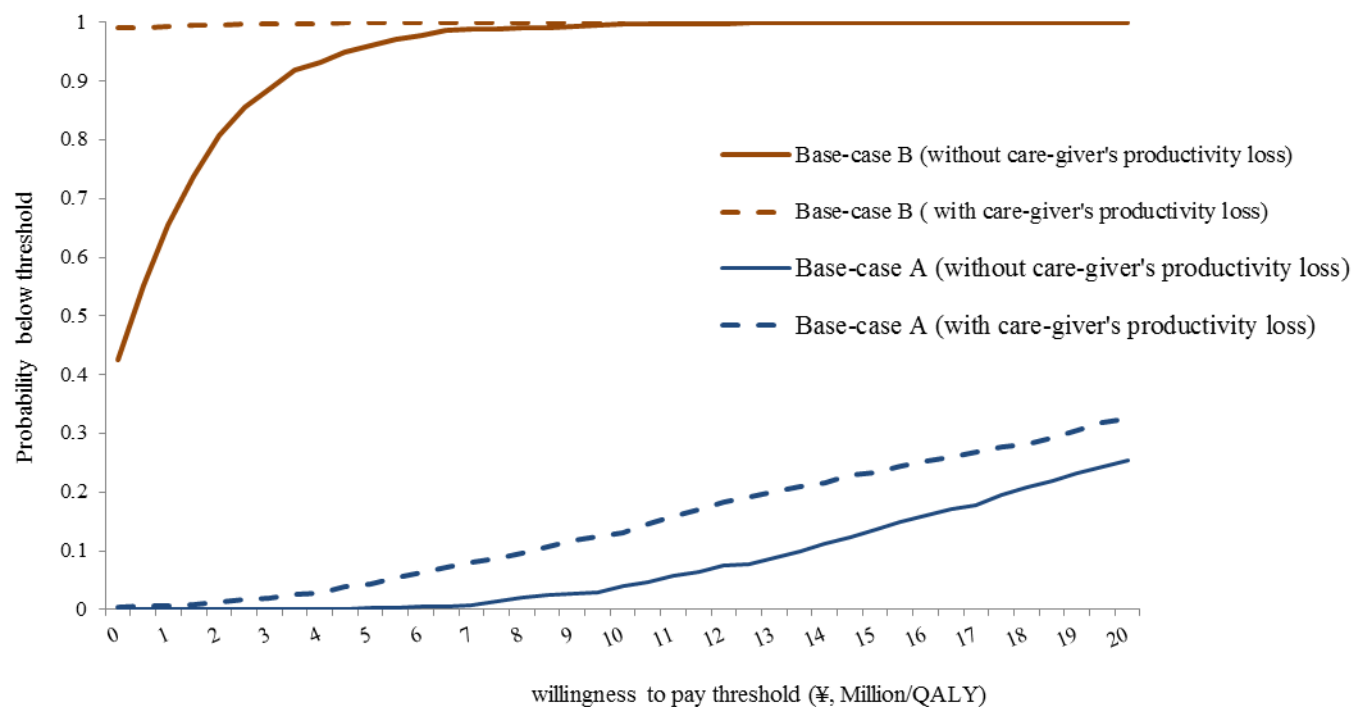Fig.3 Sensitivity analyses performed on vaccine effectiveness

Fig. 4. Cost-effectiveness acceptability curves (CEACs) for Base-cases with/without care-giver's productivity loss
CEAC is a commonly used visual aid for communicating the results of probabilistic sensitivity analysis in cost-effectiveness models, which presents relative cost-effectiveness as a function of the threshold ICER. The graphed value of any comparator at a particular willingness-to-pay represents the probability that it is cost-effective, based on the uncertainties included in the simulation.