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

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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 hospitalised radiograph-confirmed 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% for 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 countries, 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 × 4h when uptaking simultaneously with Hib vaccine. 1/2 × 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 ¥5,426,124 (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.

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References


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


### Table 1. Epidemiological data used on model

<table>
<thead>
<tr>
<th>Variable</th>
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<td>Bacteraemia</td>
<td>0.21</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0.11</td>
</tr>
<tr>
<td>Hospitalised pneumonia</td>
<td>0.11</td>
</tr>
<tr>
<td>Vaccine effectiveness (VE) of PCV-7*; %</td>
<td>80.0</td>
</tr>
<tr>
<td>In reducing vaccine serotype IPD</td>
<td>54.0</td>
</tr>
<tr>
<td>In reducing vaccine serotype AOM</td>
<td>27.0</td>
</tr>
<tr>
<td>Proportion of IPD episodes due to PCV-7 serotype; %</td>
<td>68.5</td>
</tr>
<tr>
<td>Proportion of IPD episodes due to PCV-13 serotype; %</td>
<td>80.9</td>
</tr>
<tr>
<td>Proportion of hospitalized CAP episodes due to PCV-7 serotype; %</td>
<td>66.7</td>
</tr>
<tr>
<td>Proportion of hospitalized CAP episodes due to PCV-13 serotype; %</td>
<td>81.0</td>
</tr>
<tr>
<td>Proportion of AOM episodes due to PCV-7 serotype; %</td>
<td>68.2</td>
</tr>
<tr>
<td>Proportion of AOM episodes due to PCV-13 serotype; %</td>
<td>86.0</td>
</tr>
<tr>
<td>Life expectancy of neurological sequelae</td>
<td>53.9</td>
</tr>
<tr>
<td>Life expectancy of Japanese population at age 5</td>
<td>74.9 male; 80.8 female</td>
</tr>
<tr>
<td>Utility weight</td>
<td>1</td>
</tr>
<tr>
<td>Healthy</td>
<td>0.9</td>
</tr>
<tr>
<td>Condition</td>
<td>Probability</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Neurological sequelae</td>
<td>0.57</td>
</tr>
<tr>
<td>Curable bacteraemia</td>
<td>0.9921</td>
</tr>
<tr>
<td>Curable meningitis</td>
<td>0.9768</td>
</tr>
<tr>
<td>Curable pneumonia</td>
<td>0.994</td>
</tr>
<tr>
<td>AOM</td>
<td>0.995</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
</tbody>
</table>

*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>
<thead>
<tr>
<th>Base-case</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-case A</td>
<td>No net indirect effect. Not effective against serotypes unique to PCV-13 (1, 3, 5, 6A, 7F, 19A)</td>
</tr>
<tr>
<td>Base-case B</td>
<td>No net indirect effect. Effective against serotypes unique to PCV-13 (1, 3, 5, 6A, 7F, 19A)</td>
</tr>
<tr>
<td>Scenario-1</td>
<td>Net indirect effect to non-vaccinated aged under 5. The effect to IPD only. No net indirect effect to aged over 5.</td>
</tr>
<tr>
<td>Scenario-2</td>
<td>Net indirect effect to non-vaccinated aged under 5. The effect to IPD, hospitalised pneumonia. No net indirect effect to aged over 5.</td>
</tr>
<tr>
<td>Scenario-3</td>
<td>Net indirect effect to non-vaccinated aged under 5. The effect to IPD, AOM. No net indirect effect to aged over 5.</td>
</tr>
<tr>
<td>Scenario-4</td>
<td>Net indirect effect to non-vaccinated aged under 5. The effect to IPD, hospitalised pneumonia, AOM. No net indirect effect to aged over 5.</td>
</tr>
</tbody>
</table>
### Table 3: Costs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per PCV-7</td>
<td>¥10,000</td>
</tr>
<tr>
<td>Cost per PCV-13</td>
<td>¥13,000</td>
</tr>
</tbody>
</table>

- **Treatment cost:**
  - Bacteraemia episode, survive
    - Age groups: 0 to <1, 1 to <2, 2 to <3, 3 to <4, 4 to <5
      - ¥419,153
      - ¥419,153
      - ¥419,153
      - ¥392,802
      - ¥392,802
    - Bacteraemia episode, death
      - ¥1,032,126
      - ¥1,032,126
      - ¥1,032,126
      - ¥1,010,205
      - ¥1,010,205
    - Meningitis episode, survive
      - ¥852,642
      - ¥852,642
      - ¥852,642
      - ¥843,867
      - ¥843,867
    - Meningitis episode, death
      - ¥1,470,421
      - ¥1,470,421
      - ¥1,479,196
      - ¥1,510,669
      - ¥1,510,669
    - Pneumonia episode
      - ¥221,133
      - ¥221,133
      - ¥221,133
      - ¥164,916
      - ¥164,916
    - AOM episode
      - ¥31,990
      - ¥31,990
      - ¥31,990
      - ¥31,990
      - ¥31,990
    - Hearing impairment (long term treatment)/year
      - ¥79,422
      - ¥79,422
      - ¥79,422
      - ¥78,057
      - ¥78,057
    - Neurological sequelae (long term treatment)/year
      - ¥420,464
      - ¥420,464
      - ¥420,464
      - ¥380,671
      - ¥380,671

- **Variables related to care-giver’s productivity loss:**
  - Frequency of outpatient visits/number of hospitalisation days
    - Bacteraemia episode
      - 2.9 visits/11.5 days
      - 2.8 visits/10.5 days
    - Meningitis episode
      - 8.1 visits/22.7 days
      - 7.8 visits/21.1 days
    - Pneumonia episode
      - 2.7 visits/6.8 days
      - 2.8 visits/4.9 days
    - Hearing impairment
      - 8 hours per day until the child is admitted to special support education system
    - Neurological sequelae
      - Absent working hours per AOM episode (h)
        - 33.6
        - 27.7
        - 50.3
        - 43.1
        - 39.4
  - Average hourly wage of Japanese women labourers
    - ¥1,328

US$1 = ¥80
### Table 4 Results of Base-case analyses

<table>
<thead>
<tr>
<th></th>
<th>Base-case A: PCV-13 with no additional VE to PCV-7 on AOM*</th>
<th>Base-case B: PCV-13 with additional VE to PCV-7 on AOM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine cost per child</td>
<td>Cost per child</td>
</tr>
<tr>
<td>No programme</td>
<td>¥0</td>
<td>¥64,346</td>
</tr>
<tr>
<td>PCV-7</td>
<td>¥28,725</td>
<td>¥49,747</td>
</tr>
<tr>
<td>PCV-13</td>
<td>¥37,342</td>
<td>¥48,975</td>
</tr>
<tr>
<td><strong>Effect per child</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QALY</td>
<td>32.8087</td>
<td>32.8152</td>
</tr>
<tr>
<td>YOLS</td>
<td>32.8109</td>
<td>32.8158</td>
</tr>
<tr>
<td><strong>CER/ICER</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without productivity loss</td>
<td>¥6,352,110</td>
<td>¥1,588,575</td>
</tr>
<tr>
<td>With productivity loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost/QALY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without productivity loss</td>
<td>¥9,034,940</td>
<td>¥4,495,903</td>
</tr>
<tr>
<td>With productivity loss</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on the package insert of Prevenar®
### Table 5 Results of Scenario analyses

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

Variables (Lower value, Upper value)

- PCV-13 reducing AOM, 1 to <2 (0.54, 0.77)
- PCV-13 reducing AOM, 2 to <3 (0.52, 0.75)
- PCV-13 reducing AOM, 0 to <1 (0.54, 0.77)
- PCV-7 reducing AOM, 1 to <2 (0.43, 0.64)
- PCV-7 reducing AOM, 0 to <1 (0.43, 0.64)
- PCV-7 reducing AOM, 2 to <3 (0.42, 0.62)
- PCV-13 reducing AOM, 3 to <4 (0.51, 0.72)
- PCV-13 reducing AOM, 4 to <5 (0.49, 0.70)
- PCV-7 reducing AOM, 3 to <4 (0.41, 0.51)
- PCV-7 reducing AOM, 4 to <5 (0.39, 0.49)
- PCV-13 reducing hospitalised pneumonia, 0 to <1 (0.27, 0.39)
- PCV-13 reducing hospitalised pneumonia, 0 to <1 (0.22, 0.328)

Base-case
ICER= ¥343,830/QALY
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.