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ORIGINAL RESEARCH

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Cost-effectiveness analysis of 20-valent pneumococcal conjugate vaccine for routine pediatric vaccination programs in Japan

Masayoshi Shinjoh [a], Kanae Togo [b], Tomoyuki Hayamizu [c], Naohiro Yonemoto [b], Junko Morii[d], Johnna Perdrizet [e] and Kazumasa Kamei [b]

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ABSTRACT

Background: The Japanese National Immunization Program currently includes the pediatric 13 valent pneumococcal conjugate vaccine (PCV13) to prevent pneumococcal infections. We aimed to evaluate the cost-effectiveness of 20-valent PCV (PCV20) as a pediatric vaccine versus PCV13.

Methods: A decision-analytic Markov model was used to estimate expected costs, quality-adjusted life-years (QALYs), and prevented cases and deaths caused by invasive pneumococcal disease, pneumonia, and acute otitis media over a ten-year time horizon from the societal and healthcare payer perspectives.

Results: PCV20 was dominant, i.e. less costly and more effective, over PCV13 (gained 294,599 QALYs and reduced Japanese yen [JPY] 352.6 billion [2.6 billion United States dollars, USD] from the societal perspective and JPY 178.9 billion [USD 1.4 billion] from the payer perspective). Sensitivity and scenario analyses validated the robustness of the base scenario results. When comparing PCV20 with PCV13, the threshold analysis revealed an incremental cost-effectiveness ratio that was within the threshold value (JPY 5 million/QALY) at a maximum acquisition cost of JPY 74,033 [USD 563] (societal perspective) and JPY 67,758 [USD 515] (payer perspective).

Conclusions: As a pediatric vaccine, PCV20 was dominant over PCV13 regardless of the study perspective.

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KEYWORDS
Cost-effectiveness; Japan; PCV20; pneumococcal disease; vaccination

1. Introduction

Pneumococcal disease (PD), caused by *Streptococcus pneumoniae (S. pneumoniae)*, remains one of the most common vaccine-preventable diseases worldwide, causing both invasive pneumococcal disease (IPD) and noninvasive disease (e.g. acute otitis media [AOM]) [1]. These infections are associated with high morbidity and mortality, specifically in infants with preexisting chronic conditions [1]. In Japan, *S. pneumoniae* is the primary cause of bacterial meningitis in infants above the age of three months [2,3]. IPD conditions are recognized as category V infectious diseases and are the subject of all-case surveillance in Japan [4].

The introduction of pneumococcal conjugate vaccines (PCVs) has been a major breakthrough in reducing the disease burden in Japan. Using PCVs is currently the most effective way to prevent pneumococcal infections. Currently, the pediatric 13-valent PCV (PCV13), which includes the purified capsular polysaccharide of 13 serotypes of *S. pneumoniae* (1, 3, 4, 5, 6A, 6B, 7F, 9 V, 14, 18C, 19A, 19F, and 23F), is administered under the Japanese National Immunization Program (NIP) to prevent pneumococcal infections. According to a nationwide population-based surveillance of IPD in Japanese children, the percentage of IPD caused by PCV13-serotypes out of the total pediatric IPD cases was 53.2% in 2013 [5]. Introduction of PCV13 into the NIP in 2013 resulted in lower cases of IPD caused by PCV13-serotypes, i.e. 8.2% in 2016 to 2.1% in 2019 and 2.3% in 2022 [5], indicating the effectiveness of PCV13 against PCV13-serotypes. However, the non-PCV13-serotype had an increased composition ratio in pathogenic bacteria due to serotype replacement (the expansion of non-vaccine serotypes resulting from the removal of vaccine-type serotypes from the population). Therefore, new vaccines are expected to be developed that are active against current non-vaccine serotypes.

There are currently at least 100 identified pneumococcal serotypes [6,7], reflecting differences in the structure of the polysaccharide capsule [8]; however, only a few result in the majority of the disease [9,10]. Higher-valent PCVs, 20-valent (PCV20) and 15-valent (PCV15), are expected to be introduced in Japan to expand serotype coverage and improve protection against PD. PCV20 includes PCV13 serotypes plus serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F [11], and an application to approve its use in children has been submitted in Japan. In contrast, in 2023, PCV15 (including PCV13 serotypes plus 22F and 33F serotypes) was approved for children by the Ministry of Health, Labour and Welfare [12]. Of note, 2022 surveillance data from 43 *S. pneumoniae* isolates collected from pediatric IPD

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cases in Japan showed that while only 2.3% and 9.3% were of PCV13 and PCV15 serotypes, respectively, a substantially higher number of serotypes were of PCV20 (30.2%) [5]. Furthermore, the additional serotypes included in PCV20 are medically significant [13–19]. To defend against these present non-vaccine serotypes, it would be advantageous to include higher-valent PCVs, particularly PCV20. This could potentially reduce the disease burden in this target population.

In Japan, in addition to the vaccine effectiveness and safety, cost-effectiveness is one of the key aspects of the inclusion of new vaccines in the NIP [20]. In other countries, such as the United States (US) and Canada, economic evaluations have shown that PCV20 could be more cost-effective than PCV13 and PCV15 [21,22]. In Japan, a cost-effectiveness analysis of PCV15 compared with PCV13 was recently published [23]. The study showed that PCV15 was dominant (less costly and more effective) over PCV13 as expected as the vaccine acquisition costs of PCV15 and PCV13 were parity although the serotype coverage of PCV15 was wider than PCV13. However, to the best of our knowledge, no cost-effectiveness analysis has been conducted to date for pediatric PCV20 in the Japanese population. Since the serotype distribution of different PCVs varies from country to country [24], an evaluation of the health and economic impact of using PCV20 in Japan will inform the inclusion of PCV20 in the NIP, as well as price adjustments. Therefore, our study aimed to ascertain the cost-effectiveness of PCV20 versus the current routine vaccine, PCV13. In addition to this, we also evaluated the cost-effectiveness of PCV15 versus PCV13 and PCV20 versus PCV15.

2. Methods

2.1. Model description, settings, and outcomes

We adopted a previously published decision-analytic Markov (state-transition) model [21] for Japanese settings to evaluate the potential health outcomes and economic impact of switching vaccination from PCV13 to PCV20 or PCV15 (Figure 1). Additionally, we also compared PCV20 with PCV15. In this model, the three primary doses were administered at 2, 3, and 4 months postpartum, followed by a booster dose at 15 months (i.e. full 3 + 1 schedule), with all doses from the same vaccine type.

In each annual model cycle, individuals could develop multiple PDs, including IPD (meningitis and bacteremia), all-cause pneumonia (hospitalized and non-hospitalized), and AOM (with or without myringotomy), could not develp PD, or could die [25]. The model considered direct vaccination effects (reduction in disease incidence caused by vaccine-type serotypes) and indirect effects (herd effects, i.e. protective effects observed in unvaccinated populations) to reflect post-vaccination transmission dynamics [26]. A time horizon of ten years was adopted, as vaccine effects generally stabilize 5–9 years following PCV implementation [27].

The model outcomes included: 1) health outcomes (number of cases by disease type and number of deaths); 2) economic outcomes (medical costs and productivity loss); and 3) cost-effectiveness outcomes (incremental costs, incremental quality-adjusted life-years [QALYs], and incremental cost-effectiveness ratios [ICERs] per QALY gained). Furthermore, the incremental net monetary benefit (INMB) was calculated as follows:

$$\begin{aligned} INMB = {} & \textit{incremental QALY swith PCV20 [or PCV15] over PCV13} \\ & \times \textit{threshold} \\ & - \textit{incremental costs with PCV20 [or PCV15] ove PCV13} \end{aligned}$$

For Japan, a threshold of 5 million Japanese yen (JPY) (38,023.39 US dollars [USD]) (exchange rate: USD 1= JPY 131.498 [28]) per QALY gained was used [29,30]. Health outcomes and costs were discounted at a rate of 2% per year [31].

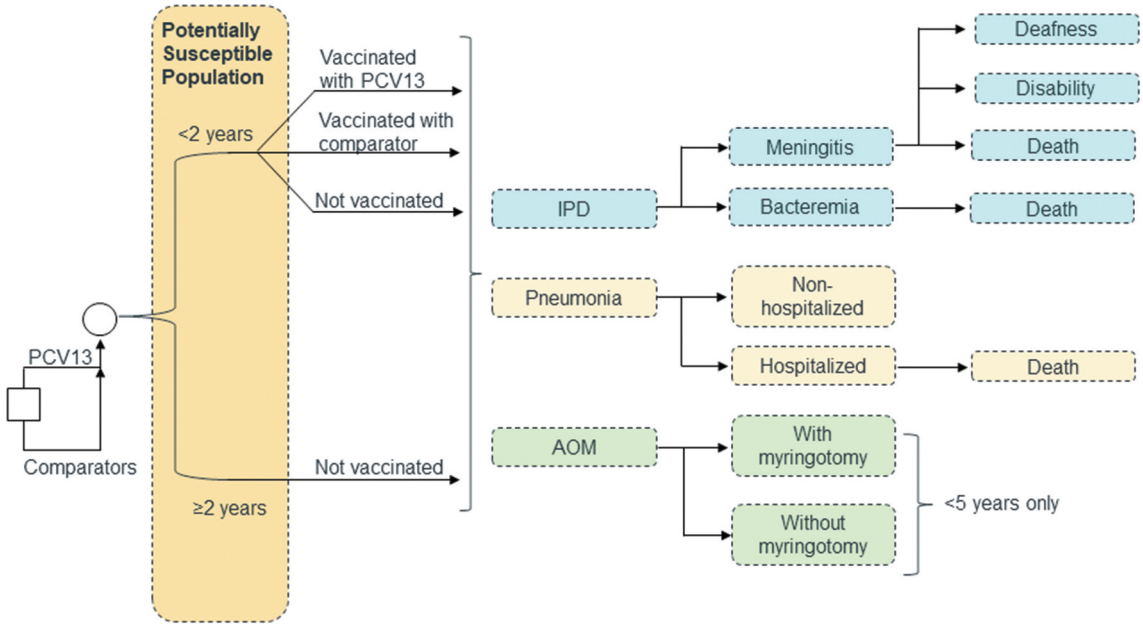


Figure 1. Model schematic.

AOM, acute otitis media; IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine.

We did not model the unvaccinated population as a comparator because the pneumococcal vaccination uptake for children was nearly 100% in Japan, according to the most recent statistics in 2021 [32].

2.2. Model inputs and data sources

The specific model parameters are presented in Table 1 and further described in Supplemental Tables 1–8. To the extent possible, relevant data from Japan were prioritized during the parameter search and used in the current analyses.

2.2.1. Population

Population size stratified by age groups (Table 1) and the size of the incoming birth cohort (Supplemental Table S1) were obtained from the Japanese Statistics Bureau [33] and the National Institute of Population and Social Security Research [55], respectively.

2.2.2. Disease incidence and serotype distribution

Considering the impact of COVID-19 on PD, disease incidence rates before the COVID-19 pandemic were chosen for the base scenario analysis (Table 1). Incidence rates for IPD were calculated based on surveillance data from the National Institute of Infectious Diseases [33,37]. Incidence rates for noninvasive diseases were estimated from the claims database of JMDC Inc., which consists of claims data from 285 employer insurance associations, including the records of approximately 16 million people [35]. The disease and procedure codes used for the analysis using the claims database are detailed in Supplemental Methods and Supplemental Table 2.

The serotype distribution of IPD in children and elderly individuals was used in this analysis [5,56] (Table 1). In the absence of robust data on noninvasive diseases, the age-specific serotype distribution of IPD was used as a proxy.

2.2.3. Mortality and sequalae

Age-specific general mortality rates were taken from Japanese life tables [57]. Published literature or publicly available data were used to estimate case fatality rates (CFRs) for meningitis [2,38], bacteremia [53], and hospitalized pneumonia [41], and the probability of developing sequalae (deafness and disability) from meningitis [43,53] (Table 1). CFRs related to non-hospitalized pneumonia or AOM and the probability of developing sequalae from other disease conditions were assumed to be zero based on prior evidence.

2.2.4. Vaccine uptake

Vaccine uptake for each vaccine under the full 3 + 1 schedule was assumed to be 97.9% for the primary doses and 97.1% for the booster dose, based on the current uptake of PCV13 for children <2 years of age in Japan [32].

2.2.5. Vaccine effectiveness

Both direct and indirect effects were included for vaccine effectiveness (Supplemental Methods). The base scenario analysis included all diseases such as IPD, pneumonia and AOM. Based on previous estimates in Europe [58,59], each vaccine was assumed to have a full direct effect for five years after administration of the final dose, while the effects waned by 10% annually at Year 6 to 42% of the original vaccine effectiveness by Year 10 (i.e. maximum duration of protection). Indirect effects were applied as a reduction in disease incidence over time against serotypes unique to PCV20 and PCV15 (versus PCV13), as they provide maximum protection for the entire population. All disease states were assumed to have the same rate of accrual of indirect effects. Indirect effects against additionally covered serotypes were calculated using a reduction in disease incidence adjusted to the ratio of serotype distribution at the time of PCV13 introduction and the current serotype distribution. In addition, serotype 3 was excluded for estimating the indirect effects. Since this serotype is more relevant for adults aged ≥65 years [60], the exclusion of serotype 3 was a conservative approach.

2.2.6. Utilities

Age- and sex-specific utilities for the general Japanese population [61] and the proportion of females in the population [33] are detailed in Supplemental Table S8. The model assumed a baseline utility of 1.0 for age groups <20 years due to a lack of data. Total utilities were calculated by considering QALY decrements for all disease states and a utility multiplier for lifetime events (disease sequalae) (Table 1).

2.2.7. Vaccination and medical costs

Vaccination costs consisted of vaccine acquisition costs and administration costs (Table 1). The vaccine acquisition cost for PCV15 was on par with that of PCV13 [62,63]. As of December 2023, PCV20 had not been approved in Japan. Therefore, for this study, we temporarily multiplied the cost of PCV13 by 1.13 to match the ratio of costs of pediatric PCV20 (USD 178.00 [JPY 23,407]) and PCV13 (USD 158.18 [JPY 20,800]) in the US [64]. The vaccine administration cost was calculated based on a fee-for-service price list (2022) by the Ministry of Health, Labour and Welfare [65] and included costs for initial consultation, infant addition, procedures, and biologics premiums.

Medical costs included the cost per episode of each disease condition and were estimated either from the JMDC database [35] (for ages <65 years) or the MDV database [52] (for ages ≥65 years) (Table 1). The MDV database contains claims data and discharge summaries from over 480 hospitals across Japan [52]. Details on calculating costs are described in the supplemental material (Supplemental Methods). Management costs of long-term sequalae (deafness and disability) were estimated from previous literature [53]. All vaccination and medical costs were adjusted to 2022 national tariffs [65], wherever applicable.

2.2.8. Costs related to productivity losses

Productivity losses were considered in the analysis from the societal perspective. Productivity losses due to vaccination included half a day off by guardians for their children's vaccination. Productivity losses due to the diseases were assumed to be incurred by guardians of patients aged <19 years,

Table 1. Model input values for base scenario analysis.

Parameters	Age group (years) 0–<1	1–<2	2–<3	3–<4	4–<5	5–17	18–34	35–49	50–64	65–<100	Sources
Population size (1,000 person)	830	836	871	915	938	13,665	21,508	25,256	24,468	36,128	[33]
Annual disease incidence (100,000 person-years)[a]											
IPD	11.04	10.22	10.22	10.22	10.22	0.54	0.34	0.85	1.99	5.46	[33,34]
Hospitalized pneumonia[b]	2,353.7	2,353.7	909.6	909.6	909.6	141.1	75.1	75.1	219.0	1,225.6	[35,36]
Non-hospitalized pneumonia[b]	7,808.2	7,808.2	8,694.4	8,694.4	8,694.4	2,231.1	1,009.0	1,009.0	1,659.2	2,395.7	[35,36]
AOM with myringotomy	1,832.1	1,832.1	866.0	866.0	866.0	–	–	–	–	–	[35]
AOM without myringotomy	27,071.7	27,071.7	27,666.9	27,666.9	27,666.9	–	–	–	–	–	[35]
Breakdown of IPD cases (%)											
Meningitis[c]	6	6	6	6	6	6	6	6	6	8	[37]
Case fatality rates (%)											
Meningitis[d]	3.7	3.7	3.7	3.7	3.7	3.7	7.1	7.1	7.1	12.1	[2,38,39]
Bacteremia[e]	4.0	4.0	4.0	4.0	4.0	4.0	13.8	13.8	13.8	19.2	[38,40]
Hospitalized pneumonia[f]	0.08	0.08	0.08	0.08	0.08	0.17	0.26	1.33	2.58	16.87	[33,35,36,41,42]
Probability of sequalae (%)											
Deafness due to meningitis[g]	2.2	2.2	2.2	2.2	2.2	2.2	4.1	7.1	6.1	6.6	[43,44]
Disability due to meningitis[g]	16.5	16.5	16.5	16.5	16.5	16.5	12.6	22.0	19.0	20.4	
Vaccine uptake, PCV13/15/20%)											
Primary doses	97.9	—	—	—	—	—	—	—	—	—	[32]
Booster dose	97.1	—	—	—	—	—	—	—	—	—	
Serotype distribution (%)[a]											
PCV13	3.1	3.1	3.1	3.1	3.1	3.1	29.2	29.2	29.2	29.2	[5]
PCV15	10.3	10.3	10.3	10.3	10.3	10.3	35.0	35.0	35.0	35.0	
PCV20	37.7	37.7	37.7	37.7	37.7	37.7	61.1	61.1	61.1	61.1	
Utility decrements											
Meningitis	0.023	0.023	0.023	0.023	0.023	0.023	0.130	0.130	0.130	0.130	[45–47]
Bacteremia	0.008	0.008	0.008	0.008	0.008	0.008	0.130	0.130	0.130	0.130	[45–47]
Hospitalized pneumonia	0.006	0.006	0.006	0.006	0.006	0.006	0.130	0.130	0.130	0.130	[45–47]
Non-hospitalized pneumonia	0.004	0.004	0.004	0.004	0.004	0.004	0.045	0.045	0.045	0.045	[45–47]
AOM (with/without myringotomy)	0.005	0.005	0.005	0.005	0.005	0.005	–	–	–	–	[45–47]
Utility multiplier for lifetime events (sequalae)											
Deafness due to meningitis					0.73						[48]
Disability due to meningitis					0.60						[49]
Vaccine costs (JPY, per dose)											
PCV13/15/20 (Base scenario A)[h]					11,600/11,600/12,502						[50,51] Assumption
PCV13/15/20 (Base scenario B)[h]					11,600/11,600/11,600						
Medical cost per episode (JPY)											
Meningitis	916,735	916,735	453,080	453,080	453,080	901,920	1,224,450	1,224,450	1,731,160	2,178,263	[35,52]
Bacteremia	706,080	706,080	720,200	720,200	720,200	1,243,500	925,585	925,585	1,280,460	1,349,205	
Hospitalized pneumonia	338,150	338,150	322,330	322,330	322,330	439,440	695,635	695,635	932,215	1,125,977	
Non-hospitalized pneumonia	28,310	28,310	24,630	24,630	24,630	22,140	28,070	28,070	33,490	43,646	
AOM with myringotomy	90,220	90,220	54,930	54,930	54,930	–	–	–	–	–	
AOM without myringotomy	24,260	24,260	18,760	18,760	18,760	–	–	–	–	–	
Lifetime medical cost per episode of sequalae (JPY)[i]											
Deafness					762,705						[53]
Disability	4,054,885	4,054,885	3,678,360	3,678,360	3,678,360	3,678,360	3,678,360	3,678,360	3,678,360	3,678,360	
Productivity losses of guardians due to vaccination (JPY, per dose)[j]											
PCV13/15/20					9,405						[35,54] Assumption

(*Continued*)

Table 1. (Continued).

Parameters	Age group (years)										Sources
	0–<1	1–<2	2–<3	3–<4	4–<5	5–17	18–34	35–49	50–64	65–<100	
Productivity loss costs due to disease (JPY, per episode)[k]											
Meningitis	235,118	235,118	235,118	235,118	235,118	357,380	432,618	432,618	583,094	583,094	[35,54]
Bacteremia	225,714	225,714	225,714	225,714	225,714	413,808	319,761	319,761	413,808	432,618	
Hospitalized pneumonia	169,285	169,285	169,285	169,285	169,285	188,095	244,523	244,523	319,761	376,189	
Non-hospitalized pneumonia	75,238	75,238	75,238	75,238	75,238	75,238	75,238	75,238	75,238	75,238	
AOM with myringotomy	56,428	56,428	56,428	56,428	56,428	–	–	–	–	–	
AOM without myringotomy	56,428	56,428	56,428	56,428	56,428	–	–	–	–	–	

AOM, acute otitis media; IPD, invasive pneumococcal disease; JPY, Japanese yen; PCV, pneumococcal conjugate vaccine.
[a]Average between 2017 and 2019.
[b]For incidence at ages 65 years and older, we multiplied the incidence at ages 50–64 years from the JMDC analysis by the relative risk at ages 65–74, 75–84, and 85 years and older estimated by Morimoto et al. 2015 [36]. We then adjusted for the Japanese population estimates.
[c]Values for ages 5–64 years were assumed to be the same as those under 5 years. The proportion of cases with meningitis among IPD was sourced from the NIID [37] and the remaining cases were assumed to be with bacteremia.
[d]Values for ages 0–17 years were calculated by summing data from Shinjoh et al. 2017 and Shinjoh et al. 2020 [2,39]; values for ages 18 years and older were from Chang et al. 2022 [38].
[e]Values for ages 0–17 years were from Nakano et al. 2020 [40]; for ages 18 and older, they were from Chang et al. 2022 [38].
[f]The number of deaths due to pneumonia in Vital Statistics was divided by the number of hospitalized pneumonia patients. The number of hospitalized pneumonia patients was calculated using Japanese population estimates based on the incidence of hospitalized pneumonia patients. The mortality rate for outpatient pneumonia was assumed to be 0.
[g]Values for ages 0–17 years were from Iwata et al. 2021 [43] and for ages 18 years and older were from Iwata et al. 2023 [44].
[h]PCV20 acquisition costs were assumed to be JPY 8,102 or JPY 7,200 in base scenarios A and B, respectively. Administration cost was assumed as JPY 4,400.
[i]The annual costs cited in Suaya et al. 2015 [53] were converted to the April 2022 reimbursement rate level for cost adjustment and multiplied by 10 years of analysis period.
[j]Productivity losses due to vaccination were calculated by multiplying the daily wage by half a day.
[k]For meningitis, bacteremia, and inpatient pneumonia, the median number of days of hospitalization from the JMDC analysis plus three days was multiplied by the average daily wage from the Basic Wage Structure Survey. For non-hospitalized pneumonia and AOM, the median number of treatment days based on expert opinion was assumed to be four and three days, respectively, and multiplied by the average daily wage.

patients themselves (19–64 years), and caregivers (for patients aged ≥65 years). A human capital approach was adopted to estimate the costs associated with productivity losses based on work force participation, number of loss days, and average daily wages [66]. Productivity losses were derived by multiplying the number of working days missed due to an episode of disease [35,53] and the wages lost due to this absence, as estimated by their average daily wages (JPY 18,809 [USD 143.04] in 2022) based on the basic survey on wage structure (Table 1) [54].

2.3. Analyses

The base scenario analyses compared PCV20 or PCV15 with PCV13 from the societal and healthcare payer perspectives. Additionally, we compared PCV20 versus PCV15. Two base scenarios were considered: A) the acquisition cost of PCV20 was JPY 8,102 and B) the acquisition cost of PCV20 was JPY 7,200. Furthermore, total 11 scenario analyses were conducted to assess uncertainty around specific model input parameters (Supplemental Table S9). A one-way sensitivity analysis (OWSA) was conducted for PCV20 versus PCV13 to identify drivers of model outcomes and examine key areas of uncertainty. The following variables were considered for the OWSA: direct and indirect vaccine effect, incidence of disease (including complication rates where relevant), CFRs, probability of sequalae, serotype coverage, PCV20 vaccine cost and other costs (except vaccine administration costs), utilities, and utility decrements. Upper and lower bounds were either based on the 95% confidence intervals derived from the data or calculated as ± 25% of the base scenario values where data were not available. The upper and lower bounds for the cost of the PCV20 vaccine were JPY 10,128 (JPY 8,102 × 1.25) and JPY 7,200 (parity to PCV13), respectively. A probabilistic sensitivity analysis (PSA) with 1000 iterations was performed to examine the impact of joint uncertainty on all input parameters. The distribution used for PSA are described in detail in Supplemental Table S10. Typical probability distributions were used in the analyses, following the guidance of Briggs et al. [67]. Additionally, threshold analysis was conducted.

3. Results

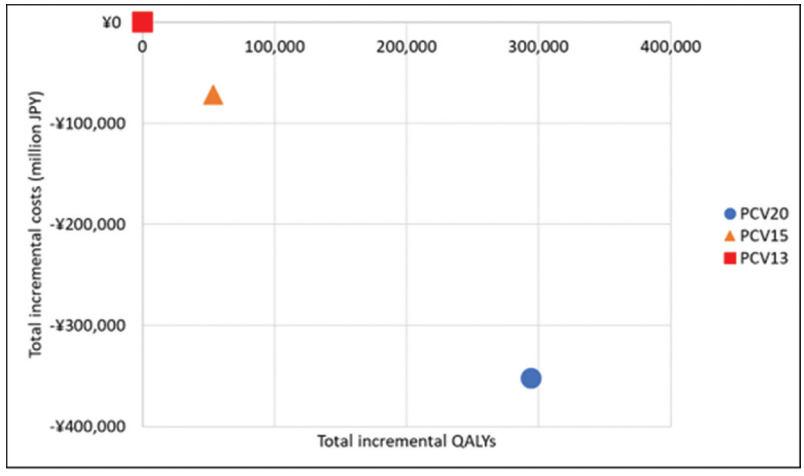
3.1. Base scenario

In base scenario A, PCV20 was more effective in comparison with PCV13 for preventing pneumococcal infections, with a gain of 294,599 QALYs per population (0.036 QALYs per person) over a time horizon of ten years (Table 2). Additionally, PCV20 reduced JPY 352,637 million (USD 2,628 million) per population and JPY 44,506 (USD 338) per person in total costs from the societal perspective. Furthermore, PCV20 reduced JPY 178,901 million (USD 1,360 million) per population and JPY 22,579 (USD 172) per person from the payer perspective. These results suggested that PCV20 could be a dominant strategy over PCV13, regardless of the study perspective (Figure 2). PCV20 prevented 9,298 cases of IPD (677 meningitis and 8,621 bacteremia); 1,508,487 cases of pneumonia (229,346 hospitalized and

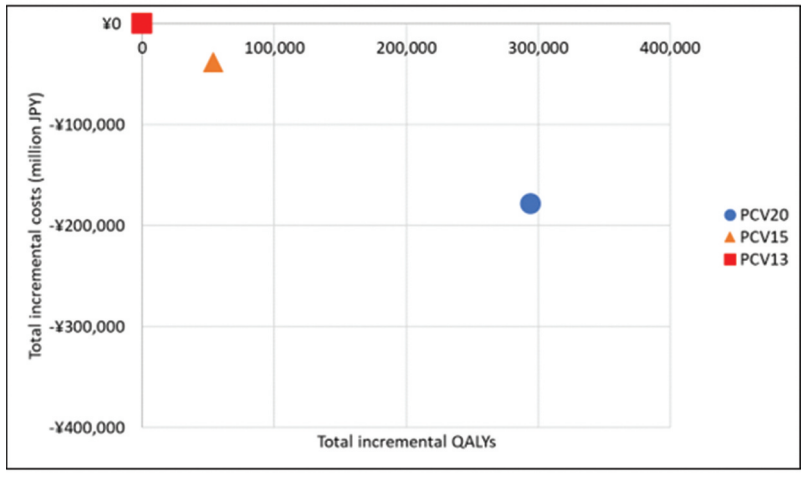
Table 2. Results of base scenario A.

Outcomes	PCV20	PCV15	PCV13	Incremental values		
				PCV20 vs. PCV13	PCV20 vs. PCV15	PCV15 vs. PCV13
QALYs						
per population	3,210,738,526	3,210,497,665	3,210,443,926	294,599	240,861	53,738
per person[a]	405.200	405.170	405.164	0.036	0.030	0.007
Total costs from societal perspective (JPY)						
per population	11,666,475,234,068	11,947,246,389,681	12,019,112,550,588	−352,637,316,521	−280,771,155,614	−71,866,160,907
per person[a]	1,472,327	1,507,763	1,516,833	−44,506	−35,436	−9,070
Total costs from payer perspective (JPY)						
per population	7,213,910,248,984	7,354,471,703,093	7,392,810,804,820	−178,900,555,837	−140,561,454,109	−38,339,101,727
per person[a]	910,406	928,147	932,986	−22,579	−17,740	−4,839
ICER (JPY/QALY gained)						
Societal perspective	—	—	—	Dominant	Dominant	Dominant
Payer perspective	—	—	—	Dominant	Dominant	Dominant

ICER, incremental cost-effectiveness ratio; JPY, Japanese yen; PCV, pneumococcal conjugate vaccine; QALY, quality-adjusted life-year.
[a]Per person outcomes were calculated by dividing the per population outcomes by the number of the vaccinated infants receiving each primary vaccine dose (7,923,835, 7,923,823 and 7,923,819 for PCV20, PCV15 and PCV13, respectively).



a)



b)

Figure 2. Cost-effectiveness plane for three vaccination programs (per population) in base scenario A.

a. Societal perspective.

b. Payer perspective.

¥/JPY , Japanese yen; PCV, pneumococcal conjugate vaccine; QALY, quality-adjusted life-year.

Table 3. Detailed incremental values in base scenarios and scenario 1 (indirect effects excluded) – societal perspective.

	Base scenario			Scenario 1 (indirect effects excluded)		
Outcomes	PCV20 vs. PCV13	PCV20 vs. PCV15	PCV15 vs. PCV13	PCV20 vs. PCV13	PCV20 vs. PCV15	PCV15 vs. PCV13
Health outcomes (number of cases)						
Meningitis	−677	−552	−125	−58	−45	−12
Bacteremia	−8,621	−7,028	−1,593	−899	−713	−187
Hospitalized pneumonia	−229,346	−185,302	−44,045	−52,136	−41,296	−10,840
Non-hospitalized pneumonia	−1,279,141	−1,034,497	−244,643	−70,373	−55,741	−14,632
AOM with myringotomy	−25,839	−20,466	−5,372	−12,778	−10,121	−2,657
AOM without myringotomy	−558,316	−442,232	−116,085	−272,217	−215,618	−56,599
Total deaths due to disease	−13,656	−11,179	−2,477	−82	−65	−17
Medical costs (JPY)						
Vaccination						
Base scenario A	24,977,315,323	24,977,123,058	192,265	24,976,979,489	24,976,852,013	127,476
Base scenario B	924,705	732,439	192,265	613,100	485,624	127,476
Treatment costs (JPY)						
Meningitis	−1,136,710,455	−929,564,703	−207,145,752	−33,895,368	−26,847,845	−7,047,524
Bacteremia	−9,363,397,653	−7,646,256,752	−1,717,140,901	−568,594,004	−450,372,060	−118,221,944
Hospitalized pneumonia	−147,237,918,649	−119,789,780,649	−27,448,138,000	−15,830,838,322	−12,539,290,512	−3,291,547,810
Non-hospitalized pneumonia	−33,482,593,752	−27,136,062,764	−6,346,530,988	−1,622,634,439	−1,285,256,676	−337,377,763
AOM with myringotomy	−1,743,438,426	−1,380,943,089	−362,495,337	−876,292,667	−694,093,817	−182,198,850
AOM without myringotomy	−10,445,976,888	−8,274,054,421	−2,171,922,467	−5,145,518,314	−4,075,662,770	−1,069,855,544
Lifetime cost of sequalae	−467,835,336	−381,914,789	−85,920,547	−33,642,762	−26,647,765	−6,994,998
Productivity losses (JPY)	−173,736,760,684	−140,209,701,504	−33,527,059,180	−27,463,455,263	−21,753,257,555	−5,710,197,708

AOM, acute otitis media; JPY, Japanese yen; PCV, pneumococcal conjugate vaccine.

Table 4. Results of base scenario B and scenario 1.

				Incremental values		
Outcomes	PCV20	PCV15	PCV13	PCV20 vs. PCV13	PCV20 vs. PCV15	PCV15 vs. PCV13
Base scenario B						
QALYs	3,210,738,526	3,210,497,665	3,210,443,926	294,599	240,861	53,738
Total costs (JPY)						
Societal perspective	11,641,498,843,449	11,947,246,389,681	12,019,112,550,588	−377,613,707,139	−305,747,546,232	−71,866,160,907
Payer perspective	7,188,933,858,365	7,354,471,703,093	7,392,810,804,820	−203,876,946,455	−165,537,844,728	−38,339,101,727
ICER (JPY/QALY gained)						
Societal perspective	—	—	—	Dominant	Dominant	Dominant
Payer perspective	—	—	—	Dominant	Dominant	Dominant
Scenario 1: Indirect effects excluded from base scenario A						
QALYs	3,210,451,322	3,210,445,464	3,210,443,926	7,396	5,858	1,538
Total costs (JPY)						
Societal perspective	11,992,514,658,938	12,008,389,235,925	12,019,112,550,588	−26,597,891,651	−15,874,576,987	−10,723,314,664
Payer perspective	7,393,676,368,433	7,387,797,687,864	7,392,810,804,820	865,563,612	5,878,680,568	−5,013,116,956
ICER (JPY/QALY gained)						
Societal perspective	—	—	—	Dominant	Dominant	Dominant
Payer perspective	—	—	—	117,032	1,003,501	Dominant
Scenario 1: Indirect effects excluded from base scenario B						
QALYs	3,210,451,322	3,210,445,464	3,210,443,926	7,396	5,858	1,538
Total costs (JPY)						
Societal perspective	11,967,538,292,549	12,008,389,235,925	12,019,112,550,588	−51,574,258,039	−40,850,943,376	−10,723,314,664
Payer perspective	7,368,700,002,044	7,387,797,687,864	7,392,810,804,820	−24,110,802,776	−19,097,685,820	−5,013,116,956
ICER (JPY/QALY gained)						
Societal perspective	—	—	—	Dominant	Dominant	Dominant
Payer perspective	—	—	—	Dominant	Dominant	Dominant

ICER, incremental cost-effectiveness ratio; JPY, Japanese yen; PCV, pneumococcal conjugate vaccine; QALY, quality-adjusted life-year.

1,279,141 non-hospitalized); 584,155 cases of AOM (25,839 with myringotomy and 558,316 without myringotomy); and 13,656 deaths compared with PCV13 (Table 3 and Supplemental Table S11). A cost-breakdown analysis showed that while PCV20 incurred an incremental vaccination cost of JPY 24,977 million (USD 190 million), the total treatment cost and productivity losses were reduced by JPY 203,878 million (USD 1,550 million) and JPY 173,737 million (USD 1,321 million), respectively. Similar results were obtained in base scenario B when the acquisition cost of PCV20 was set at par with those of PCV13 and PCV15 (Table 4).

Finally, when PCV20 was compared with PCV15, PCV20 was found to be more effective (gained 240,861 QALYs per population) and reduced costs by JPY 280,771 million (USD 2,135 million) and JPY 140,561 million (USD 1,069 million) per population from the societal and payer perspectives, respectively (Table 2).

3.2. Scenario analyses

Tables 4 and 5 show the results of scenario analyses, where nine input parameters were varied in 11 scenarios and their impact analyzed on the outcomes with PCV20 versus PCV13. In all scenario analyses expect scenario 1 from the payer perspective, PCV20 was dominant (i.e. less costly and more effective) regardless of the study perspective. In the scenario

Table 5. Results of scenario analyses for PCV20 versus PCV13.

Parameters and scenario settings	Incremental values			ICER (JPY/QALY gained)		INMB (JPY)	
	QALY	Medical costs	Productivity losses	Societal perspective	Payer perspective	Societal perspective	Payer perspective
Base scenario A (reference)	294,599	−178,900,555,837	−173,736,760,684	Dominant	Dominant	1,825,632,747,748	1,651,895,987,065
Include indirect effects							
IPD only (Scenario 2)	34,490	−9,419,971,640	−30,606,501,299	Dominant	Dominant	212,478,242,615	39,219,325,398
Incidence and serotype distribution							
Apply data from COVID-19 era (Scenario 3)	195,912	−96,201,062,013	−88,097,606,136	Dominant	Dominant	1,163,859,863,975	1,075,762,257,839
Vaccine uptake							
100% (Scenario 4)	294,715	−178,828,592,831	−174,367,366,497	Dominant	Dominant	1,826,770,078,509	1,652,402,712,012
95% (Scenario 5)	294,498	−179,146,167,027	−173,205,931,586	Dominant	Dominant	1,824,841,676,896	1,651,635,745,310
Direct effect for those aged < 1							
Full direct effect (Scenario 6)	295,011	−180,712,260,018	−175,495,791,792	Dominant	Dominant	1,831,262,332,809	1,655,766,541,017
Productivity loss costs							
Apply employment rate and proportion of patients 65+ who require help (Scenario 7)	294,599	−178,900,555,837	−118,899,993,775	Dominant	Dominant	1,770,795,980,840	1,651,895,987,065
Include probability of sequelae							
Not considered (Scenario 8)	293,791	−178,432,720,501	−173,736,760,684	Dominant	Dominant	1,821,126,895,854	1,647,390,135,171
QALY decrement							
Apply utility multipliers (Scenario 9)	278,585	−178,900,555,837	−173,736,760,684	Dominant	Dominant	1,745,561,405,568	1,571,824,644,885
CFRs for meningitis, bacteremia							
Data from Kakenhi [68] (Scenario 10)	292,179	−178,901,855,019	−173,739,055,881	Dominant	Dominant	1,813,536,511,767	1,639,797,455,886
Incidence and cost data of AOM							
Data from Yamanaka et al. 2009 [69] (Scenario 11)	299,277	−225,297,113,154	−226,535,213,606	Dominant	Dominant	1,948,219,544,927	1,721,684,331,322

AOM, acute otitis media; CFRs, case fatality rates; COVID-19, coronavirus disease 2019; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; IPD, invasive pneumococcal disease; JPY, Japanese yen; PCV, pneumococcal conjugate vaccine; QALY, quality-adjusted life-year.

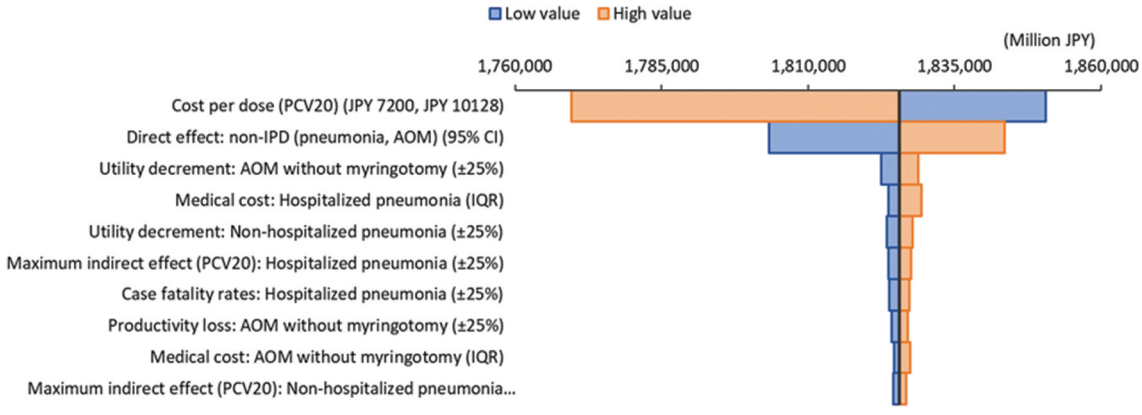


Figure 3. Tornado plot for PCV20 vs. PCV13 (INMB).

AOM, acute otitis media; CI, confidence interval; INMB, incremental net monetary benefit; IPD, invasive pneumococcal disease; IQR, interquartile range; JPY, Japanese yen; PCV, pneumococcal conjugate vaccine.

1, the ICER for PCV20 compared to PCV13 was JPY 117,032/QALY which was below JPY 5 million/QALY (the threshold value in Japan [29]) from the payer perspective. Thus, the results of the base scenarios were found to be robust.

Considering only direct effects for all diseases such as IPD, pneumonia and AOM (i.e. exclusion of indirect effects) (Scenario 1), considering direct effects for all disease and indirect effects only for IPD (Scenario 2), and utilizing the incidence and serotype distribution from the COVID-19 era (Scenario 3) had the highest impact on INMB. In the base case, INMB was calculated as JPY 1,826 billion (USD 14 billion) [incremental QALYs (294,599 QALYs) × threshold (JPY 5 million/QALY) – incremental costs (JPY −352.6 billion)] from the societal perspective. INMB was JPY 64 billion (USD 487 million) in Scenario 1, JPY 212 billion (USD 2 billion) in Scenario 2 and JPY 1,164 billion (USD 9 billion) in Scenario 3, respectively. The results of Scenario 11, where incidence and cost data of AOM were used from Yamanaka et al. [69], prevented a greater number of cases of AOM at a higher cost benefit compared with the base scenario results (Supplemental Table S12).

3.3. Sensitivity analyses

The INMB values in OWSA for PCV20 versus PCV13 from the societal perspective are presented as a tornado diagram (Figure 3). The factors that had the highest impact on the INMB for PCV20 versus PCV13 were PCV20 vaccine cost, followed by the vaccine's direct effects on pneumonia and AOM. Positive INMB values in all cases confirmed the robustness of

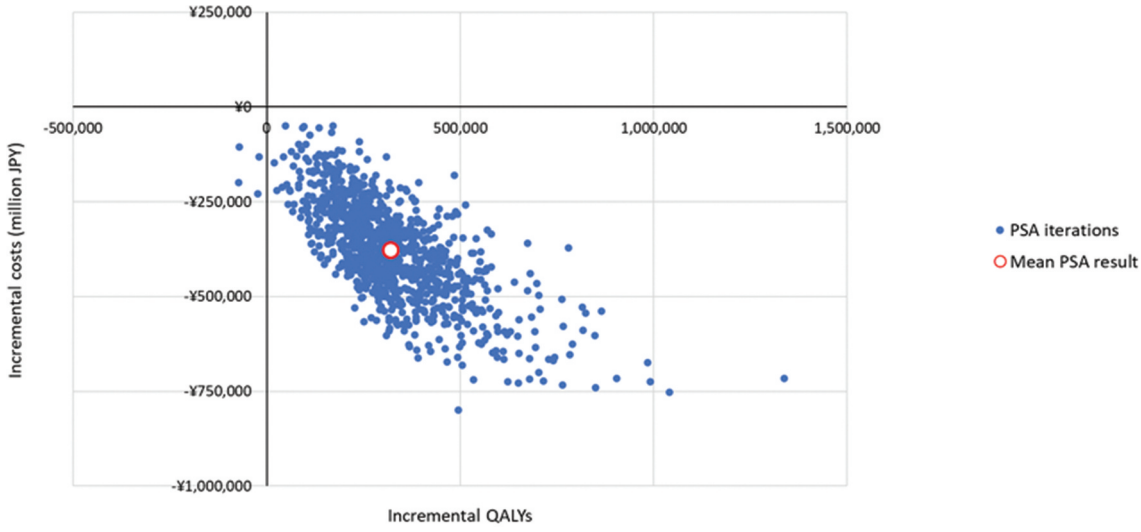


Figure 4. PSA scatterplot for PCV20 vs. PCV13.

¥/JPY, Japanese yen; PCV, pneumococcal conjugate vaccine; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

our base scenario results, indicating that PCV20 is a dominant strategy over PCV13.

PSA results showed that when PCV20 was compared with PCV13, most simulations were in the southeast quadrant (99.6%), indicating higher QALYs at lower costs (Figure 4). The PSA results were complemented with a cost-effectiveness acceptability curve that showed the probability of PCV20 being accepted was 98.5% under a threshold of JPY 5 million/QALY when comparing the three vaccines (Supplemental Figure S2).

3.4. Threshold analysis

Threshold analysis of the acquisition cost of PCV20 showed that the ICER values for PCV20 versus PCV13 continued to be dominant at a maximum cost of JPY 20,837 (USD 158) from the societal perspective and JPY 14,562 (USD 111) from the payer perspective. Moreover, the cost remained below the threshold value for Japan (JPY 5 million/QALY) at a maximum acquisition cost for PCV20 of JPY 74,033 (USD 563) from the societal perspective and JPY 67,758 (USD 515) from the payer perspective.

4. Discussion

Our base scenario results suggested that vaccination with PCV20 prevented pneumococcal infections and deaths while incurring lower costs in comparison with PCV13 and PCV15. Therefore, PCV20, at the assumed acquisition cost of JPY 8,102, can be considered a dominant strategy over PCV13 and PCV15 from both the societal and payer perspectives, as it provides wider serotype coverage than lower-valent vaccines. The robustness of our base scenario results was further validated by scenario and sensitivity analyses.

The scenario that had the greatest impact on health and cost outcomes was the exclusion of indirect effects. The estimation of the indirect effects of vaccines may not always be easy to capture [70]. Moreover, due to a lack of published data in Japan, global data were used to estimate these effects in the base scenario analysis. Therefore, we evaluated an alternate scenario where indirect effects were not included as a conservative approach. Athough this scenario had the greatest impact on ICER, PCV20 was still dominant over PCV13 from a societal perspective and resulted in an ICER less than the threshold of JPY 5 million per QALY gained from a payer perspective. However, it is evident from several reports that PCVs exert an indirect effect (herd immunity) [26,71], and therefore this scenario can be considered an extreme example.

During the COVID-19 pandemic (2020–2022), the incidence rate of community-acquired pneumonia, including pneumococcal pneumonia, was markedly reduced due to several safety measures that were applied globally to curb the spread of coronavirus infection [72,73]. However, as COVID-19 converges gradually, pneumococcal infection rates are anticipated to increase [74]. Therefore, this study employed the incidence and serotype distribution data before the COVID-19 period (2017–2019) for the base scenario analysis. In contrast, after experiencing COVID-19, residents' awareness of preventing infectious diseases may have been altered, and the incidence of pneumococcal infections may continue to be low [72]. We assessed the impact of these changes in disease incidence on our base scenario results by performing a scenario analysis that used the lower PD incidence during the COVID-19 era (2020–2022). The results of this scenario showed that the base scenario cost-effectiveness outcomes remained unchanged as a dominant strategy.

For the base scenario analysis in this study, AOM was defined as either with or without myringotomy, which was different than the categorization used in a previous study in Japan [69] (complex AOM and simple AOM). Therefore, we conducted a scenario analysis using incidence and cost data for complex and simple AOM from Yamanaka et al. [69]. This analysis showed that PCV20 was a dominant strategy over PCV13. However, since Yamanaka et al. used incidence data from a previous study conducted in the US during 2000–2004

[75], caution should be exercised when applying this result to Japanese settings.

As of December 2023, the application for approval to use of PCV20 as a pediatric vaccine has been submitted in Japan, and the acquisition cost for PCV20 was still unknown. In this study, we temporarily set it as JPY 8,102 for base scenario A and JPY 7,200 (parity to PCV13) for base scenario B. In both base scenarios, PCV20 was found to be dominant over PCV13. Furthermore, threshold analysis revealed that the ICER was still under JPY 5 million/QALY in comparison with PCV13 when the acquisition cost of PCV20 was set at JPY 74,033 from the societal perspective and JPY 67,758 from the payer perspective. These results will be informative for future discussions about the PCV20 price and its inclusion in the Japanese NIP.

There are several ways to value lost productivity. The human capital approach was used in this study because the approach is commonly used and recommended in many pharmacoeconomic guidelines including Japan [31,76]. One of the other interesting approaches is to estimate the society's loss because of less productivity caused by the absence of adults or of parents caring for sick children and losing days from work. However, our study result indicated that PCV20 was dominant, being associated with less cost and greater effectiveness, in both societal and payer perspectives (i.e. with and without productivity loss). Therefore, scenario analysis with another approach for evaluation of productivity losses was not conducted in this study.

To the best of our knowledge, this is the first analysis evaluating the cost-effectiveness of the pediatric PCV20 vaccination strategy using epidemiologic data, including serotype distribution, in Japan. Our study strengthens previous evidence from other countries on the impact of vaccinating with PCV20 despite using a relatively different population setting, epidemiological information, and vaccine prices [21,22,77–80]. For example, in the US, vaccination with PCV20 was shown to result in an ICER ranging from cost-saving to USD 125,000/QALY compared with PCV13 in children aged <2 years, and therefore, the Pneumococcal Vaccines Work Group recommended the routine use of PCV20 in this population in June 2023 [77]. Similar to PCV20, our study results are also in alignment with the recently published cost-effectiveness analysis of PCV15 compared with PCV13 in Japan, which reported PCV15 to be a dominant strategy over PCV13 for pediatric vaccination from both the societal and payer perspectives [23].

The results of this study must be interpreted in the context of a few limitations related to the study design, particularly around the availability of inputs used to populate the model. First, the decision-analytic model is a simplified representation of disease transmission and outcomes in PD and may not represent the complete heterogeneity of the health care delivery system. We mitigated this by using age stratification and by including the indirect effects of the vaccines. Second, in line with other published studies, multiple sources were used to derive the direct and indirect effects of vaccines for each health state, thereby introducing some bias regarding interpretation and data synthesis. As the direct effectiveness data of PCV15 and PCV20 was limited, it was assumed that the direct effectiveness of PCV13, PCV15, and PCV20 would be same against the serotypes included in the vaccines, i.e. serotype-specific effectiveness was not considered in the model due to the lack of robust data. It is therefore essential to review the vaccine effectiveness as more evidence on PCV15 and PCV20 accumulates. Third, we assumed the serotype distribution for each vaccine to be the same for IPD and noninvasive diseases; however, there could be unaccounted differences. Sensitivity analyses confirmed that the outcomes remained unchanged after using alternative parameters. Fourth, our study did not consider the serotype replacement, which is the reduction in cases of PD caused by vaccine-type serotypes of PCV15 and PCV20 after their introduction. The outcomes could have been overestimated as we used the same values for the serotype distribution and incidence over the ten years of analysis. In the future, it will be crucial to closely monitor the distribution of emerging serotypes after the introduction of the PCV15 and PCV20 vaccines. Last, the probability distributions around a few parameters in PSA might be subjective because they were based on extrapolation and secondary data synthesis. Nonetheless, the combination of scenario and sensitivity analyses provided evidence that the conclusions reported in this study were robust.

5. Conclusions

From the societal and payer perspectives, PCV20 was estimated to be a dominant vaccination strategy over PCV13 for protecting children against pneumococcal infections in Japan. In the future, PCV20 is expected to replace PCV13 in the routine vaccination program in Japan, where there are fiscal challenges to curb rapidly increasing medical costs.

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Declaration of interest

M Shinjoh has no relevant affiliations or financial involvement with any other organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. However, outside this study, M Shinjoh has received speaking honoraria from Meiji Seika Pharma Co., Ltd., Shionogi & Co., Ltd., MSD K.K., FUJIREBIO Inc., Mitsubishi Tanabe Pharma Corporation, Taisho Pharmaceutical Co., Ltd., FUJIFILM Toyama Chemical Co., Ltd., The Mainichi Newspapers Co., Ltd., Maruho Co., Ltd., Astellas Pharma Inc., Sumitomo Pharma Co., Ltd., Daiichi Sankyo Co., Ltd., Takeda Pharmaceutical Co., Ltd., Japan Vaccine, a consultation fee from Pfizer Japan Inc., and grant support from JSPS KAKENHI, Japan (Grant Number JP20K10546, 2020–2023), none of which was in connection with the work presented here. K Togo, N Yonemoto, T Hayamizu, and K Kamei are employees of Pfizer Japan Inc. J Morii is an employee of IQVIA Solutions G.K., and J Perdrizet is an employee of Pfizer Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or material discussed in the manuscript apart from those disclosed.

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Author contributions

All the authors (M Shinjoh, K Togo, T Hayamizu, N Yonemoto, J Morii, J Perdrizet, K Kamei) (1) made substantial contributions to the study concept or the data analysis or interpretation, (2) drafted the manuscript or revised it critically for important intellectual content, (3) approved the final version of the manuscript to be published, and (4) agreed to be accountable for all aspects of the work.

Ethical approval

This study used publicly available or anonymized data; therefore, ethical approval was not required.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article or its supplemental materials.

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