

## Burden of illness associated with pneumococcal infections in Japan - a targeted literature review

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### ABSTRACT

**Introduction:** Pneumococcal diseases (PDs) are among the leading causes of mortality and morbidity worldwide. However, the evidence on epidemiology, health economic, and patient-reported outcomes has not been systematically reviewed and published in Japan. This study aimed to assess the burden, treatment adherence and compliance, and serotype distribution associated with PDs in Japan.

**Method:** One hundred and eight studies were identified between January 2005 and June 2020. The identified studies were mostly regional and with a limited scale, clinical settings, and populations.

**Results:** In 2013–2017, invasive PD incidence rates were 4.98–9.47/100,000 in <4-year-olds, 0.36/100,000 in 5–14-year-olds, 0.46/100,000 in 15–64-year-olds, and 1.50–5.38/100,000 in the elderly. The incidence of invasive PDs in children decreased from 24.6/100,000 in 2008 to 10.7/100,000 in 2013 after the introduction of PCV7 and further declined to 10.3/100,000 in 2014 after PCV13 was introduced. From 2014, the prevalence of PCV13 serotypes decreased across all age groups along with a decrease of PPV23 serotypes, but an increase of PPV23 serotypes not included in PCV13 among adults and the elderly. No study reported health-related quality-of-life data for PDs. In children, direct costs were 340,905–405,978 JPY (3,099–3,691 USD) per pneumococcal bacteraemia, 767,447–848,255 JPY (6,977–7,711 USD) per pneumococcal meningitis, and 79,000 JPY (718 USD) per pneumococcal acute otitis media episodes. In adults and the elderly, the direct cost of pneumococcal pneumonia was 348,280–389,630 JPY (3,166–3,542 USD). The average hospital stay length was 7.2–31.9 days in children, 9.0 days in adults and 9.0–28.7 days in adults and the elderly.

**Conclusions:** The epidemiological burden of PDs remains high in Japan, especially among children and the elderly with invasive PDs accounting for a very small proportion of all PDs. A significant impact of the PCV13 vaccine program was reported, while the PPV23's impact remains unclear. A substantial decrease in quality-adjusted life years in adults and the elderly and a high economic burden may exist.

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## Introduction

*Streptococcus pneumoniae* (*Pneumococcus*) can cause a range of illnesses such as ear infections to serious sepsis, meningitis, and pneumonia with bacteremia or without bacteremia [1]. Infections with *S. pneumoniae*, named pneumococcal diseases, affect people of all ages, particularly those with underlying illnesses, and pose a major threat [2]. According to the World Health Organization (WHO), pneumococcal diseases are one of the leading causes of mortality and morbidity. It is estimated that up to 1.6 million people die of pneumococcal diseases each year globally, especially young children and the elderly who tend to have more severe symptoms and complications in comparison to adults [3]. In Japan, the Ministry of Health, Labour and Welfare in the statistics for 2019 identifies pneumonia as the 5th most common

cause of death in individuals  $\geq 65$  years of age, and the 4th most common cause of death in individuals  $\geq 75$  years of age [4]. Pneumococcal infections can also result in long-term problems, such as brain damage or hearing loss [5]. Pneumococcal diseases are classified into invasive pneumococcal diseases (IPDs) and non-invasive pneumococcal diseases (non-IPDs), defined by how the bacteria invade parts of the body that are normally sterile. A non-IPD occurs outside of the tissues and fluids of major organs or the blood, while an IPD occurs inside the tissues and fluids of major organs or the blood. In general, IPDs are associated with more severe manifestations than non-IPDs [3], whereas non-IPDs have a much higher incidence in the elderly and people with a weakened immune system [6]. Therefore, both IPDs and non-IPDs are clinically serious infections.

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Given the heavy burden of pneumococcal diseases on morbidity and mortality, in April 2013, the Ministry of Health, Labour and Welfare (MHLW) designated IPDs as a notifiable disease by the Infectious Diseases Control Law [7].

MHLW has also introduced multiple pneumococcal vaccination programs since 2006 for children and the elderly (Table 1) [8]. The pneumococcal conjugate vaccine (PCV) 7 was first introduced voluntarily for young children below the age of 5 years by a governmental subsidy in November 2010 [9]. PCV7 was then officially incorporated into the national immunization program in April 2013 [10]. Subsequently, PCV13 was introduced and replaced PCV7 in November 2013 [11]. The use of PCV13 expanded to adults of 65 years or older in June 2014 [12]. In October 2014, PPV23 was introduced in Japan's national immunization program for the elderly [13]. PCV10 was approved for use in children up to 5 years of age in March 2015 [14], although it had yet to be launched on the market in Japan at the time of writing this manuscript (October 2020) [15]. In parallel, a national surveillance system in Japan collects and makes available data on IPDs, yet a national surveillance system for other pneumococcal diseases, including non-IPDs has not been established to date. As a result, surveillance by individual investigators has started in recent years and data on the burden of non-IPDs, such as pneumococcal pneumonia, are gradually being collected [6,16].

Epidemiology, health economic, and patient-reported outcomes are important outcomes for evaluating pneumococcal vaccine programs by decision-makers. Such evidence in Japan has continuously been updated over the years but has not been systematically reviewed and published. Therefore, the objective of the study was to

assess the epidemiological, humanistic, and economic burden, as well as treatment adherence and compliance and serotype distribution associated with pneumococcal diseases in Japan.

## Methods

The search was performed in the Medline database (access via the OVID interface) and the ICHUSHI database. Additionally, the Database of Grants-in-Aid for Scientific Research (KAKEN) [17] and the National Institute of Infectious Diseases (NIID) [18] websites were searched. Only publications in English and Japanese and studies published between January 2005 and June 2020 were considered. The list of titles, abstracts and full texts were screened by one reviewer according to the defined inclusion and exclusion criteria, in order to select relevant articles pertaining to the topic of interest. Search strategies are presented in Supplementary Table 1–Supplementary Table 6. A simplified search strategy was used for hand searches. 'Pneumococcus' was used as the free search term for clinical studies and results were limited to only completed studies (KAKEN, NIID). The inclusion criteria are reported as per the PICOS criteria and presented in Supplementary Table 7. Cost-effectiveness analyses with source data not meeting the inclusion criteria were excluded from the study even if the target population of the cost-effectiveness analysis (CEA) met the inclusion criteria.

When reporting outcomes, point estimate is reported if only one data point from a study was identified and a range is reported if several data points from one or more studies were identified. The findings are categorized by study types. For

**Table 1.** Timings of approved and publicly funded main vaccines.

Status	PCV7	PCV10	PCV13	PPV23†
Approved (Children)	October 2009 ( $\leq 9$ years old)	March 2015	June 2013	October 2006 ( $\geq 2$ years old)
Approved (Adults)	NA	NA	June 2014 ( $\geq 65$ years old only), May 2020 (All ages with high-risk conditions)	October 2006
Publicly funded (Children)	April 2013	NA	November 2013	NA
Publicly funded (Adults)	NA	NA	NA	October 2014
Source	<ul style="list-style-type: none"> <li>Pharmaceutical and Food Safety Bureau, MHLW [61],</li> <li>Pharmaceutical Safety Committee of the Pharmaceutical Affairs and Food Sanitation Council, MHLW [62]</li> </ul>	Pharmaceutical and Food Safety Bureau, MHLW [63]	PMDA [64]	PMDA [65]

MHLW: Ministry of Health, Labour and Welfare; NA: Not applicable; PMDA: Pharmaceuticals and Medical Devices Agency  
†PNEUMOVAX® NP.

epidemiology, including incidence, prevalence, and serotype distribution, and economic burden, the following categories are used: all, nationwide or multi-prefecture, large sample size ( $N \geq 400$ ), and PD types (IPD, all other PDs). Specifically for epidemiology, nationwide or multi-prefecture and large sample size ( $N \geq 400$ ) studies are further categorized into general and specific populations. In this study, the general population is defined as an overall population of the respective study location that includes both healthy and unhealthy people whereas a specific population is defined as those with specific conditions, hospitalized or with community-acquired pneumonia (CAP). For humanistic burdens, the following categories are used: all, nationwide or multi-prefecture, and large sample size ( $N \geq 400$ ).

For the JPY to USD conversion, a rate of 1 USD = 110 JPY is used (as of 17 September 2021) [19].

## Results

A total of 108 studies were identified across all three domains. The majority of the studies were small scale, regional studies, with limited clinical settings and populations. The included studies varied greatly with respect to population, studied diseases, geographical areas, time-periods, clinical settings, and sample size, leading to a wide range of values for all outcomes.

### Epidemiology review

Overall, 96 studies were identified, of which 36 were on children, 41 were on children and adolescents, 12 were on adults, 24 were on adults and the elderly, 19 were on the elderly, and 14 were on all ages (with no age limitation). Regarding reported indices, 69% (66) of studies reported serotype distribution, 35% (34 studies) derived prevalence, and 24% (23 studies) provided incidence. No studies reporting outcomes related to treatment adherence and compliance were identified. [Figure 1A](#) depicts the flow of information through the literature search on the epidemiology of pneumococcal diseases. [Table 2](#) depicts the results of the epidemiology review.

### Incidence

According to nationwide or multi-prefecture surveillance studies, the annual reported numbers of overall incidence of IPDs from 2013 to 2017 were 4.98–9.47 per 100,000 population for children between the ages of 0 and 4 years, 0.36 per 100,000 population for children and adolescents between the ages of 5 and 14 years (from April 2013 to Mar 2014), 0.46 per 100,000

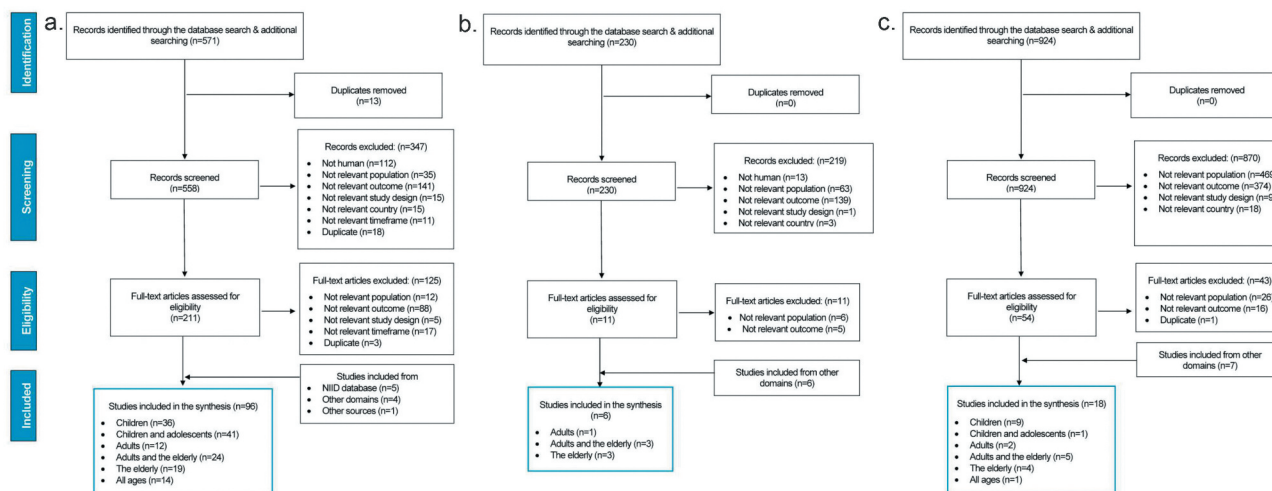
population for adults between the ages of 15 and 64 years (from April 2013 to Mar 2014), and 1.50–5.38 per 100,000 population for the elderly (from 2013 to 2017) [8,20]. They also showed a consistent increase in the numbers of reported IPD cases for children and the elderly after 2013 [8].

In children, studies on the incidence of IPDs, covering time periods before and after the introduction of PCV7 in 2010, showed a reduction from 24.6 cases per 100,000 population in 2008 to 10.7 cases per 100,000 population in 2013 [21]. After the switch from PCV7 to PCV13 in 2013, the incidence of IPDs further decreased to 10.3 in 2014 [21]. Thereafter, the incidence of IPDs showed a gradual increase at about half of the level before the PCV7 introduction [21]. Similar trends of a significant reduction in IPD incidence after the introduction of PCV7 were observed in subsequent years [22]. Conversely, in the elderly, the reported number of IPDs continuously increased from 1.50 cases to 5.38 cases per 100,000 population between 2013 and 2017 [8].

The incidence of community-onset pneumonia (COP) caused by *S. pneumoniae* for adults was reported to be 0.8–3.8 cases per 1,000 population in 15–64-year-olds and 5.1–16.9 cases per 1,000 population aged  $\geq 65$  years in 2012 [6]. Based on the data available, it can be shown that IPD accounts for a very small proportion of all pneumococcal disease. For example, in adults  $\geq 65$  years, IPD accounts for approximately 1% of all pneumococcal diseases at most [6,8].

### Prevalence

No studies reporting the prevalence of population-based IPD/non-IPD such as surveillance were identified and most of the identified studies reported data for those who have a specific disease/symptom/pathogen among a specific population. According to a large sample size survey conducted at emergency departments between 2002 and 2015, the prevalence of patients with a positive blood culture for *S. pneumoniae* in children aged 3–36 months old was 0.79% of 22,951 blood samples [23]. Higher prevalence rates of patients with blood culture positive for *S. pneumoniae* were reported in Chiba (one of the prefectures in eastern part of Japan): 1.2% among 410 children aged  $< 5$  years hospitalized for CAP between April 2008 and March 2009 in Chiba [24] and 0.6% of 7,140 blood samples taken from patients aged up to 15 years of age between 2010 and 2016 [25]. The prevalence of adults and the elderly with a positive sputum culture for *S. pneumoniae* in patients with COP aged  $\geq 15$  years was as high as 9% between September 2001 and January 2013 [6]. Conversely,



**Figure 1.** PRISMA diagram of the search results for the epidemiology (A), humanistic burden (B) and economic burden (C) review.

administrative database analysis reported similar results of the prevalence of IPDs among hospitalized CAP patients aged  $\geq 65$  years at 1.3% between June 2014 and May 2015 [26].

### Serotype distribution

The serotype distribution presented similar trends over time across all age groups.

In children, before the introduction of PCV7 in 2010, the prevalence rates of PCV7 and PCV13 serotypes were as follows: 70.6%–81.3% among IPDs [22,27–31] and 62.7%–68.4% among all other PDs [24,32,33] for PCV7 serotypes; and 83.1% among IPDs [28–30] and 80.4%–86.0% among all other PDs [24,32] for PCV13 serotypes. After the switch from PCV7 to PCV13 in 2013, PCV7 and PCV13 type serotypes became less prevalent (0% among IPDs [21,34,35] and nearly 0% among all other PDs, including acute otitis media [36–38] for PCV7 serotypes; 4.0%–5.0% among IPDs [21,34] and 19.1% among all other PDs [36–38] for PCV13 serotypes).

In children and adolescents, PCV7 and PCV13 serotypes were also reported to be prevalent before 2010 (66.7% [39]–100% [40] among IPDs and 49.3% [41]–69.1% [42] among all other PDs for PCV7 serotypes; 81.0%–100.0% [39] among IPDs and 70.6% [41]–83.2% [42] among all other PDs for PCV13 serotypes). Similar to children, after the introduction of PCV7 and PCV13 in 2013, the vaccine-type serotypes also became less prevalent (0.0% [25,34,36,43]–2.3% [44] among IPDs and 0.0% [45–48]–7.1% [49] among all other PDs for PCV7 serotypes; 0.0% [25]–20.0% [34] among IPDs and 6.2% [47]–30.0% [45] among all other PDs for PCV13 serotypes). When considering nationwide and multi-

prefectural studies only, PCV7 and PCV13 serotypes among IPDs before 2010 were reported to be 71.8% [27]–75.4% [50] and 93.7% [50], but decreased to 0.0% [36]–2.3% [44] and 7.0% [36]–17.2% [44] after 2013, respectively.

The NIID reported serotype coverages of PCV13 and PPV23 for IPD adults aged 15 years and over and the elderly between 2013 and 2017 [51]. PCV13 serotype coverage started at 43.7% in 2013, went down to 30.1% in 2016 and then became stable at around 30% in 2017. In contrast, PPV23 serotype coverage started at 64.0% in 2013, then increased to 69.0% in 2014, and gradually decreased to 63.5% in 2017 [51]. Furthermore, PCV13 serotypes in patients with IPDs decreased from 74.1% between April 2010 and March 2011 to 41.3% from April 2014 to March 2017, around the time period of the pediatric vaccine programs [44]. At the same time, PPV23 serotypes also decreased over time from 86.5% in 2010–2011 to 75.0% between 2011 and 2014 and further down to 69.1% between 2014 and 2017 [44]. On the contrary, PPV23 serotypes not included in PCV13 increased from 12.4% between 2010 and 2011 to 27.8% between 2014 and 2017 [44].

A similar trend of PCV13 and PPV23 serotypes was observed in studies focusing on the elderly after 2013 [52]. They also reported a significant reduction in PCV13 serotypes, a decrease of PPV23 serotypes, and an increase of PPV23 serotypes not included in PCV13 [52].

### Humanistic burden review

None of the included studies presented results related to health-related quality-of-life (HRQoL) for pneumococcal diseases and only studies on patient

**Table 2. Summary of studies for the epidemiology review.**

	Nationwide or multi-prefecture						All other PDs		
	All	All	General population	Specific population	All	General population		Specific population	IPDs
<b>Incidence</b>									
Children	[8,20–22,24,30,31,39,70–80]	[8,20–22,31,70]	[8,20–22,31]	[70]	[23,24,33,84]	NI	[23,24,33,84]	[8,20–22,30,31,39,70–76,78–80]	[24,77]
Children and adolescents	[20,39,79]	[20]	[20]	NI	[25,39,45,70,88,90–88,90–92]	NI	[25,39,45,70,88,90–92]	[20]	[6,81]
Adults	[6,20,81]	[6,20]	[6,20]	NI	[6,81,84,93]	NI	[6,81,84,93]	NI	[81]
Adults and the elderly	[81]	NI	NI	NI	[6,94,95,98,102]	NI	[6,94,95,98,102]	[8,20,82]	[6,81]
The elderly	[6,8,20,81,82]	[6,8,20]	[6,8,20]	NI	[26,84,103,104]	NI	[26,84,103,104]	[8,20]	[6,81]
All ages	[8,20,83]	[8,20,83]	[8,20,83]	NI	[84]	NI	[84]	[8,20]	[83]
<b>Prevalence</b>									
Children	[23,24,33,75,76,84–86]	[33,86]	NI	[33,86]	[23,24,33,84]	NI	[23,24,33,84]	[75,76,86]	[23,24,33,84–86]
Children and adolescents	[25,39,45,70,76,87–92]	[70,92]	NI	[70,92]	[25,39,45,70,88,90–88,90–92]	NI	[25,39,45,70,88,90–92]	[70,76,87]	[25,39,45,88–92]
Adults	[6,81,84,93]	[6]	NI	[6]	[84]	NI	[84]	NI	[6,81,84,93]
Adults and the elderly	[6,81,94–102]	[6,95]	NI	[6,95]	[6,94,95,98,102]	NI	[6,94,95,98,102]	NI	[6,81,94–102]
The elderly	[6,26,81,84,93,103,104]	[6,103]	NI	[6,103]	[26,84,103,104]	NI	[26,84,103,104]	[26]	[6,81,84,93,103,104]
All ages	[84,105]	NI	NI	NI	[84]	NI	[84]	NI	[84,105]
<b>Serotype distribution†</b>									
Children	[21,22,24,27–38,71,74,106–108]	[21,22,27,29,31–33,36,37,107,108]	NA	NA	[22,27,36,108]	NA	[22,27,36,108]	[21,22,27–31,34–36,71,74,108]	[24,32,33,36–38,106,107]
Children and adolescents	[25,27–29,32,34,36,37,39–50,70,72,76,89–91,106,108–116]	[27,29,32,36,37,41,42,44,46,50,70,108,112,115]	NA	NA	[27,36,41,44,47,48,108,111,112,114]	NA	[27,36,41,44,47,48,108,111,112,114]	[25,27–29,34,36,39,40,43,44,50,70,72,76,108–110,112,113]	[32,36,37,41,42,45–49,89–91,106,109–112,114–116]
Adults	[34,38,46,55,115,117]	[46,55,115,117]	NA	NA	NI	NA	NI	[34,117]	[34,38,46,55,115]
Adults and the elderly	[44,50,51,82,110,111,114,118–123]	[44,50,51,119,120,122,123]	NA	NA	[44,51,111,114,119,120,122,123]	NA	[44,51,111,114,119,120,122,123]	[44,50,51,82,110,118,121,123]	[110,111,114,119,120,122]
The elderly	[34,35,38,46,52,55,103,115,117,124]	[46,55,103,115,117]	NA	NA	[103]	NA	[103]	[118,121,123]	[38,46,52,55,103,115,124]
All ages	[34,35,38,110,111,114,125–127]	[125–127]	NA	NA	[35,38,111,114,126]	NA	[35,38,111,114,126]	[34,35,117]	[38,110,111,114,126,127]
<b>Treatment</b>	NI	NI	NI	NI	NI	NI	NI	NI	NI
<b>adherence/compliance</b>									

IPDs: Invasive pneumococcal diseases; NI: Not identified; NA: Not applicable; PDs: Pneumococcal diseases

\*Sample size for studies on incidence is not reported due to large variability depending on the study population.

†While Hotomi, Nakajima [129], Yamagishi, Mikamo [129], and Takano, Ozaki [92] met the inclusion criteria and therefore were included in Table 3 and PRISMA, their data were not analyzed in the serotype distribution sections in this manuscript and therefore they were not included in this table as the studies did not report detailed data on vaccine type serotypes.



reported outcomes were identified. However, CAP severity staging scales such as A-DROP, CURB65, and the Pneumonia Severity Index (PSI), were reported in 6 studies for adults and the elderly. Figure 1B depicts the flow of information through the literature search on the humanistic burden. Among adults, the mean scores for PSI and CURB65 were estimated as 28.2 and 0.5, respectively [53]. Among adults and the elderly, the proportion of patients with pneumococcal pneumonia with a severe and moderate stage measured by PSI were estimated 21.3% [54]–23.4% [52] and 37.1% [54]–41.5% [52], respectively. The elderly reported more severe results than adults, with the estimated mean scores for PSI and CURB65 of 105.6 and 1.9, respectively [53]. The proportion of elderly patients with a CURB65 of 3 (severe) was estimated to be 61.0% [55]. Table 3 presents the results of a humanistic burden review.

### Economic burden review

Overall, 18 studies were identified. Half of the studies (n = 9) focused on children, 1 study focused on children and adolescents, 4 studies focused on adults and the elderly, 4 studies focused on the elderly, and 1 study focused on all ages (no age limit). Sixteen studies reported outcomes related to resource use, followed by direct costs (8 studies), indirect costs (2 studies), and productivity loss (2 studies). No studies reporting indirect costs or productivity loss for adults and the elderly were identified. Figure 1C shows the flow chart of the study selection process focused on the economic burden, while a summary of the studies selected is presented in Table 4.

### Direct costs

In children, direct costs per episode were estimated at 340,905 [56]–405,978 JPY [57] for pneumococcal bacteremia, 767,447 [56]–848,255 JPY [57] for pneumococcal meningitis, and around 79,000 JPY for pneumococcal acute otitis media [56,58]. Higher direct costs for death cases were reported for pneumococcal bacteremia (1,010,205–1,032,126 JPY [57]) and for pneumococcal meningitis (1,470,421–1,510,669 JPY [57]). In adults and the elderly, direct costs of pneumococcal pneumonia were reported to be 348,280–389,630 JPY [59]. In the elderly, direct costs of pneumococcal pneumonia and CAP with IPD were estimated at 788,343 JPY [60] and 864,405 JPY [26]<sup>1</sup>, respectively.

**Table 3.** Summary of studies for the humanistic burden review.

	All	Nationwide or multi-prefecture	N ≥ 400
<b>HRQoL</b>			
Children	NI	NI	NI
Children and adolescents	NI	NI	NI
Adults	NI	NI	NI
Adults and the elderly	NI	NI	NI
The elderly	NI	NI	NI
All ages	NI	NI	NI
<b>Other PROs</b>			
Children	NI	NI	NI
Children and adolescents	NI	NI	NI
Adults	[53]	NI	NI
Adults and the elderly	[52,54,130]	[130]	NI
The elderly	[26,53,55]	[26,55]	[26,55]
All ages	NI	NI	NI
<b>Patients' satisfaction</b>			
Children	NI	NI	NI
Children and adolescents	NI	NI	NI
Adults	NI	NI	NI
Adults and the elderly	NI	NI	NI
The elderly	NI	NI	NI
All ages	NI	NI	NI

HRQoL: Health-related quality-of-life; NI: Not identified; PROs: Patient-reported outcomes.

### Indirect costs

Indirect costs were only reported for children. Indirect costs related to pneumococcal bacteremia, meningitis, and pneumonia were estimated at 122,176 JPY, 241,164 JPY [58] and 104,455 JPY [61], respectively.

### Productivity loss

Productivity loss was only reported for children's caregivers. The productivity loss of hospitalized pneumococcal bacteremia and meningitis cases were reported to be 7.9 days [56] – 11.5 days [58] and 14.6 days [56] – 22.7 days per episode [58], respectively.

### Resource use

The average length of hospital stay (ALOS) in children was estimated at 7.2 [56] – 11.5 days [57] for pneumococcal bacteremia and 13.8 [56] – 31.9 days [57] for pneumococcal meningitis. In adults, ALOS was estimated at 9.0 days [53] for pneumococcal pneumonia, while in adults and the elderly, at 9.0 [59]–16.4 days [62] for pneumococcal pneumonia and CAP caused by *S. pneumoniae* combined and 28.7 days [63] for pneumococcal bacteremia. Other studies reported data on the number of visits to general practitioners and drug

<sup>1</sup>The cost estimates were taken from the additional file of Konomura et al. [25]. While USD is used in the main text as the unit of the cost estimates, no unit was mentioned in the additional file. Therefore, we assume that the unit used in the additional file is in JPY.

**Table 4.** Summary of the studies for the economic burden review.

	All	Nationwide or multi-prefecture	N ≥ 400	IPDs	Other PDs (including unspecified)
<b>Direct costs</b>					
Children	[56–58,84,131]	[57,131]	NI	[56,57]	[58,84,131]
Children and adolescents	NI	NI	NI	NI	NI
Adults	[84]	NI	NI	NI	[84]
Adults and the elderly	[59,132]	NI	NI	NI	[59,132]
The elderly	[26,60,84]	[26,60]	[26]	[26]	[60,84]
All ages	[84]	NI	NI	NI	[84]
<b>Indirect costs</b>					
Children	[58,131]	[131]	NI	[58]	[131]
Children and adolescents	NI	NI	NI	NI	NI
Adults	NI	NI	NI	NI	NI
Adults and the elderly	NI	NI	NI	NI	NI
The elderly	NI	NI	NI	NI	NI
All ages	NI	NI	NI	NI	NI
<b>Resource use</b>					
Children	[23,56,57,84,86,133,134]	[57,86,133]	NI	[56,57,133]	[23,84,86,134]
Children and adolescents	[70]	[70]	NI	[70]	NI
Adults	[53,84]	NI	NI	NI	[53,84]
Adults and the elderly	[54,59,94,130,132]	[130]	NI	[130]	[54,59,94,132]
The elderly	[26,53,60,84]	[26,60]	[26]	[26]	[53,60,84]
All ages	[84]	NI	NI	NI	[84]
<b>Productivity loss</b>					
Children	[56,58]	NI	NI	[56,58]	NI
Children and adolescents	NI	NI	NI	NI	NI
Adults	NI	NI	NI	NI	NI
Adults and the elderly	NI	NI	NI	NI	NI
The elderly	NI	NI	NI	NI	NI
All ages	NI	NI	NI	NI	NI

IPDs: Invasive pneumococcal diseases; NI: Not identified; PDs: Pneumococcal diseases

use. Among children, the number of visits to general practitioners per episode was estimated at 1.4 [64] – 2.9 [57] for pneumococcal bacteremia and 1.5 [64] – 8.1 [57] for pneumococcal meningitis [65].

## Discussion

The epidemiological burden of pneumococcal diseases remains high in Japan, especially among children and the elderly. A significant reduction in the incidence of pediatric IPDs was observed after the PCV7 and PCV13 vaccine programs. Conversely, similar trend was not observed for IPDs on the elderly after the PPV23 vaccine program; in fact, the incidence of IPDs among the elderly increased after 2013 [8]. Further studies are needed to better understand the potential impact of the pneumococcal vaccination program among the elderly. It is expected that the impact of vaccination programs would depend on the coverage rates of PCV13 and PPV23 among the target population. Under the National Immunization Program, the coverage rates of PPV23 vaccine for the elderly were reported as 32–38% after 2014 and PCV13 vaccine for children as 95–100% (after 2013) [66]. Another study reported the coverage of PPV23 and PCV13 vaccines for elderly in 2018 as 32% and 0.7%, respectively [67]. Also, of note, case definition of IPD has changed in November 2016 with the addition of the detection of

bacteria from other sterile sites other than blood and spinal fluid to the notification criteria. While this change has only resulted in 13 cases (0.2%) in 2016 and has not had much impact at this time, careful monitoring of the trend may be required to assess its impact [68].

Vaccination programs have also changed the serotype distribution. After the introduction of PCV7 and PCV13 into the national immunization program, the PCV13 serotype coverage in pediatric IPDs considerably declined. Similarly, after the introduction of PPV23 into the national immunization program, the PPV23 serotype coverage in IPDs in the elderly also decreased. However, when examined in detail, limited data showed that the serotype coverage of PPV23 serotypes not included in PCV13 steadily increased during the same time period. Herd immunity of the PCV13 vaccination in children may have contributed to this trend. A change in serotype distribution would have a huge impact on the overall efficacy and cost-effectiveness of a particular vaccination policy. Therefore, up-to-date data on serotype distribution would be crucial for decision makers around the National Immunization Program.

The present literature review did not identify any studies on HRQoL and only studies on patient reported outcomes were identified for the humanistic burden review. Nevertheless, when studies beyond the scope of this literature review are examined, studies could be

found like Glick et al. that recently reported HRQoL outcomes in Japanese adults and elderly people with CAP [16]. QALYs were collected using the Japanese version of the EuroQol-5D-5 L health-state classification instrument at days 0, 7, 15, 30, 90, 180 and 365 after a pneumonia diagnosis from participants enrolled between 2017 and 2018. The adjusted EuroQol-5D-5 L scores were 0.759 at day 30, 0.561 at diagnosis, 0.702 by day 180 and 0.689 by day 365. Pneumonia resulted in a mean adjusted loss of 0.13 QALYs at 365 days [16]. In another study from Belgium, IPDs resulted in a loss in QALY over a year at 0.0203 in patients between the ages of 50 and 64 years and 0.1741 in patients  $\geq 65$  years of age [69].

Limited data on the economic burden related to pneumococcal diseases suggest a high burden posed on patients, with direct costs ranging from 340,905 to 405,978 JPY (3,099–3,691 USD) and from 767,447 to 848,255 JPY (6,977–7,711 USD) for pneumococcal bacteremia and meningitis, respectively. Complications due to pneumococcal diseases, namely neurological sequelae and hearing loss, as well as death, have the highest economic burden, which lead to increased costs [56,58]. Regarding resource use among children, ALOS was estimated as 7.2 [56]–11.5 days [56] for pneumococcal bacteremia and 13.8 [56]–31.9 days [57] for pneumococcal meningitis. Among adults and the elderly, ALOS was estimated as 9.0 [59]–16.4 days [62] for pneumococcal pneumonia and CAP caused by *S. pneumoniae* combined and 28.7 days [63] for pneumococcal bacteremia.

The limitation of the present review is the heterogeneity of the studies included in terms of population, studied diseases, geographical areas, time-periods, clinical settings, methods, and sample size, as well as limited data available in certain domains (e.g., on economic burden) resulting in a high degree of data variations, which might cause difficulties in providing conclusive evidence on the magnitude of the burden or the impact of vaccine programs (e.g., on serotype distribution). This is especially true for non-IPDs where a national surveillance system has not been established to date in Japan. A comprehensive national surveillance system may be needed including prevalence, not only for IPDs but also for non-IPDs. Furthermore, heterogeneity may lead to potential biases, posing challenges to the generalizability of the findings. Despite these limitations, our findings reveal important data on the burden of pneumococcal diseases, which may support the management of vaccination programs among different age groups in Japan. Currently, pneumococcal vaccines with greater serotype coverage are being developed worldwide for children and the elderly. Then, updated

information such as serotype distributions and HRQoL data would be crucial for decision makers of the National Immunization Program.

## Conclusions

The epidemiological burden of pneumococcal diseases remains high in Japan, especially among children and the elderly. Given the heavy burden of pneumococcal disease, especially CAP, prevention via vaccination is a crucial tool to control the outbreak of the disease. Coordinated effort to collect evidence on all types of PDs may greatly contribute to the assessment of the disease burden as well as overall efficacy and cost-effectiveness of vaccination programs. Continued discussions on the required data needs would be beneficial in making effective policy decisions. According to the trend of serotype distributions, a significant reduction in the PCV13 serotypes was observed, while it was unclear for non-PCV13 serotypes of PPV23. Although other sources indicate a substantial decrease in QALYs in the adult and elderly Japanese populations suffering from CAP, no evidence was found on the effect of pneumococcal diseases on HRQoL, which warrants further studies in a real-world setting. A high economic burden of pneumococcal diseases may exist despite only limited evidence being available.

## Article highlights

- The study investigates the burden of pneumococcal diseases on the Japanese population by age groups.
- The review presents comprehensive data on epidemiology; humanistic and economic burden; treatment adherence and compliance; and serotype distribution associated with pneumococcal diseases in Japan.
- The heterogeneity of the studies included may hamper the assessment of the magnitude of the burden and limit the generalizability of the findings.

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