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Risk of pneumococcal diseases in adults 19 years and older with underlying medical conditions in Japan: a retrospective, cohort study

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Appendix 1. ICD-10 codes

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ABSTRACT

Objectives: To quantify the risk of pneumococcal pneumonia (PP) and invasive pneumococcal disease (IPD) in adults aged 19 years and older with underlying medical conditions in Japan compared with healthy adults of the same age.

Design: An observational, retrospective, cohort study using two healthcare claims databases in Japan, the Japan Medical Data Center database and the Medical Data Vision database.

Participants: A total of 10.4 million individuals, representing 9.3 million person-years of follow-up, were included in the analysis. Eleven medical conditions as well as PP and IPD were identified by ICD-10 diagnostic codes and/or local disease codes used in Japan.

Primary outcome measures: Adjusted rate ratios (RRs) for PP and IPD in adults with a medical condition vs. adults without any medical condition were calculated using multivariate Poisson regression models with age and/or sex as covariates.

Results: Adults 19 years and older with an underlying medical condition (RR for PP: 1.7–13.4, RR for IPD:4.4–43.3), adults with two or more medical conditions (RR for PP: 2.8–11.6, RR for IPD: 5.8–18.7), and immunocompromised adults (RR for PP: 1.8–12.9, RR for IPD: 4.0–29.7) had a greater risk of PP and IPD compared with their healthy counterparts. Adults aged between 50 and 64 years with an underlying medical condition (PP rate:38.6–212.1 per 100,000 person-years) had a higher rate of PP than those aged ≥65 years without any condition (PP rate: 13.2–93.0 per 100,000 person-years).

Conclusions: Adults of all ages with an underlying medical condition are at greater risk of PP and IPD compared with adults without any medical condition. This risk increases with the number of underlying medical conditions. Our results support extending pneumococcal vaccination to younger adults with an underlying medical condition, especially those aged between 50 and 64 years.

Keywords: pneumococcal pneumonia, invasive, pneumococcal disease, chronic medical condition

Article summary

- **Strengths and limitations of this study:** Given the well-known differences in the genetic makeup of the Japanese population, data specific to Japan are important to formulate a national immunisation strategy and to protect vulnerable populations.
- Our study results may contribute to further knowledge on the risk of pneumococcal disease in Japanese individuals aged 19 years and older with an underlying medical condition.
- As this study was a retrospective analysis based on insurance claims data, the coding of medical conditions and episodes of pneumococcal pneumonia and invasive pneumococcal disease by ICD-10 codes may lead to misclassification, and pneumococcal pneumonia may be under-coded.
- These analyses did not consider potential confounders other than age and sex, such as pneumococcal vaccination history and residential environment, which might significantly influence the risk of pneumococcal pneumonia and invasive pneumococcal disease.
- Results from only one database cannot be extrapolated to the general population of adults in Japan, and subjects in the two databases may be representative of different adult populations.

INTRODUCTION

Pneumococcal disease, caused by encapsulated *Streptococcus pneumoniae*, is a major cause of community-acquired pneumonia, meningitis, septicaemia, osteomyelitis, septic arthritis, and bacteraemia worldwide. Older adults and children, as well as immunosuppressed individuals, such as those with HIV, are susceptible to pneumococcal disease.[1,2] In addition, adults with certain chronic medical conditions, such as diabetes, chronic lung disease, and chronic heart disease, are also at increased risk of pneumococcal disease.[3,4] These high-risk groups have been targeted for pneumococcal vaccination to reduce the burden of pneumococcal disease in many countries, including the US, Canada, the UK, and Germany.[5-8]

The 23-valent pneumococcal polysaccharide vaccine (PPV23) was licensed in 1988 in Japan, and studies have revealed the protective effects of PPV23 against invasive pneumococcal disease (IPD) and pneumococcal pneumonia (PP).[9-12] Since 2014,[13] the National Immunization Program in Japan has implemented the use of PPV23 for adults aged between 60 and 64 years with underlying medical conditions, in addition to adults aged ≥65 years. Since 2007,[14,15] the Japanese Respiratory Society has advocated an expansion of the program to individuals aged between 2 and 64 years with chronic or immunosuppressive conditions.

Several studies have been conducted in the US and Germany to examine the burden of pneumococcal disease in persons with underlying medical conditions.[16,17] A retrospective analysis of three healthcare claims repositories in the US showed that PP and IPD rates were approximately three times higher in immunocompetent adults with one or more chronic conditions (“at-risk” adults) compared with age-matched healthy adults. Additionally, these rates were approximately four to seven times and four to 10 times higher in adults who were immunocompromised or receiving immunosuppressive therapy (“high-risk” adults), respectively, compared with age-matched healthy adults.[4] A separate study using the same databases demonstrated that associated healthcare costs for IPD were approximately three

to four times and five to 10 times higher in at-risk adults and high-risk adults, respectively, compared with age-matched healthy counterparts.[18]

The risk of pneumococcal disease in individuals with underlying medical conditions is not well characterised in Japan. As differences in the genetic makeup of the Japanese population may lead to different risk patterns of pneumococcal disease compared with other countries, information specific to Japan is important not only for healthcare professionals to identify patients at increased risk of pneumococcal disease, but also for policy makers to formulate a national immunisation strategy to protect vulnerable populations. Therefore, the objective of this study was to quantify the burden of pneumococcal disease in adults aged 19 years and older with an underlying medical condition in Japan.

METHODS

Data source

Two healthcare claims databases, the Japan Medical Data Center (JMDC) database and the Medical Data Vision Company (MDV) database, were used in our study. The JMDC database contains claims data from the Japanese union-managed health insurance system, comprising 10 insurance societies since 2005. The JMDC database includes workers (mostly aged <65 years) employed by mid- to large-sized companies and their dependents, and excludes individuals aged ≥75 years. It has records of more than 3 million individuals.[19] The MDV database contains health insurance claims, administrative data, and laboratory values stored in the electronic records of 16 secondary hospitals with an average of 300 beds, which represented 9% of acute care hospitals in Japan. This database contains records for 7.4 million individuals who received healthcare services at these hospitals since 2003.[20,21] Subjects in the MDV database can be lost to follow-up. Both databases have been used in multiple studies published in peer-reviewed journals.[22-24]

Study design and population

This was an observational, retrospective, cohort study. The study design was based on those of the studies by Shea et al (2014)[4] and Weycker et al (2016)[18] conducted in the US, and that by Pelton et al (2014) conducted in Germany.[25] The study period spanned from 1 January 2006 to 31 December 2014 for the JMDC database and from 1 January 2009 to 31 December 2014 for the MDV database. Adults were included in each yearly cohort if they were aged ≥19 years on the first day of the calendar year and were continuously enrolled over the period from 1 year before to 1 year after 1 January of the calendar years 2007 to 2014 for the JMDC database and 2009 to 2014 for the MDV database.

Adults were classified as healthy or having an underlying medical condition based on whether they had the medical conditions of interest during the year preceding 1 January of each calendar year included in the study. If a patient had multiple conditions of interest in the previous year, the patient was assigned to all diagnosed conditions. Subjects without evidence of these conditions were classified as healthy. For each yearly cohort, episodes of pneumococcal disease were identified during the 1-year period from 1 January to 31 December. Multiple yearly cohorts were identified at the beginning of each calendar year during the study period. Subjects who met the inclusion criteria in multiple calendar years were included in corresponding yearly cohorts. The study design is summarised in Supplementary Figure 1.

Study variables

According to guidelines and recommendations in the US, England, and Japan,[7,13,14,26] this study included 11 medical conditions of interest: chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, chronic renal disease, cancer, HIV/AIDS, functional or anatomic asplenia, organ transplantation, alcoholism, and cerebrospinal fluid leakage. At-risk conditions in immunocompetent adults included chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, and alcoholism. High-risk immunosuppressive conditions included chronic renal disease, cancer, HIV/AIDS, functional or anatomic asplenia, organ transplantation, and cerebrospinal fluid leakage. Medical

conditions were identified by the International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10) diagnostic codes and/or local disease codes as defined by the Ministry of Health, Labour and Welfare (MHLW) in Japan.[27] Detailed definitions of each medical condition are described in Appendix 1.

Adults were classified as healthy or having an underlying medical condition based on whether they had the medical conditions of interest during the 1-year period preceding follow-up. Adults were classified as having a confirmed medical condition if at least two ICD-10 codes for the condition were recorded in the preceding calendar year. If a patient had multiple conditions of interest in the 1-year period preceding follow-up, the patient was assigned to all diagnosed conditions. Adults without evidence of these conditions were classified as healthy. In addition, adults were classified by the number of medical conditions of interest (0, 1, and 2+ conditions), risk status (healthy, immunocompetent with at-risk conditions, and immunocompromised with high-risk conditions), age (19–49, 50–64, and ≥65 years), and sex (male, female), based on the recommendations for pneumococcal vaccination by the MHLW in Japan,[13] and the recommending bodies in other countries, including the US,[5,28] England,[7] and Germany.[8]

Episodes of PP and IPD were identified by the ICD-10 diagnostic codes and/or local disease codes defined by the MHLW in Japan[27] in each calendar year. Episodes were considered distinct if they were separated by an interval of 90 days.[4] Detailed definitions of PP and IPD are described in Appendix 1.

Statistical analysis

PP and IPD rates per 100,000 person-years were calculated for the overall sample and by age, sex, medical condition, number of medical conditions, and risk status. Unadjusted rate ratios (RRs) of PP and IPD in adults with and without a medical condition were calculated by comparing the rates of PP and IPD between adults with and those without a medical condition. Multivariate Poisson regression models, with age and/or sex as

covariates, were used to determine age-and-sex-adjusted or sex-adjusted RRs of PP and IPD. Analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC, US).

Ethical statement

This study was approved by the ethics committee of Kameda Medical Center, Chiba, Japan, in October 2015, before the initiation of this study.

RESULTS

Characteristics of the study population

A total of 10.4 million individuals, representing 9.3 million person-years of follow-up, were included in the analysis (comprising 6.7 million person-years from the JMDC databases and 2.6 million person-years from the MDV database). In the JMDC database, 78% of adults were aged between 19 and 49 years, 20% were aged between 50 and 64 years, and 2% were aged ≥65 years. Further, 56% were men, 89% had no medical condition, 3% had two or more conditions, 10% were immunocompetent with at-risk conditions, and 3% were immunocompromised with high-risk conditions. In the MDV database, 18% of adults were aged between 19 and 49 years, 26% were aged between 50 and 64 years, and 55% were aged ≥65 years. Further, 46% were men, and 48% had no medical condition, 23% had two or more conditions, 40% were immunocompetent with at-risk conditions, and 22% were immunocompromised with high-risk conditions. Few study subjects with HIV/AIDS, alcoholism, asplenia, organ transplantation, and cerebrospinal fluid leakage were identified in both databases. Characteristics of the study subjects from the JMDC and MDV databases are shown in Supplementary Table 1.

The burden of pneumococcal pneumonia and invasive pneumococcal disease

Rates and RRs for PP are shown in Table 1 for the JMDC database and in Table 2 for the MDV database. Rates and RRs for IPD are shown in Table 3 for the JMDC database and in Table 4 for the MDV database.

In both databases, PP and IPD rates increased with age. In the JMDC database, the rate of PP increased from 8.3 per 100,000 person-years in adults aged between 19 and 49 years to 21.6 and 78.0 per 100,000 person-years in adults aged between 50 and 64 years and those aged ≥65 years, respectively. The rate of IPD increased from 0.5 per 100,000 person-years in adults aged between 19 and 49 years to 3.3 and 4.9 per 100,000 person-years in adults aged between 50 and 64 years and ≥65 years, respectively. In the MDV database, the rate of PP increased from 24.9 per 100,000 person-years to 46.8 and 150.8 per 100,000 person-years in adults aged between 50 and 64 years and those aged ≥65 years, respectively. The IPD rate increased from 1.5 per 100,000 person-years in adults aged between 19 and 49 years to 3.8 and 5.9 per 100,000 person-years in adults aged between 50 and 64 years and those aged ≥65 years, respectively.

Compared with healthy adults of the same age in the JMDC database, the risk of PP in younger and older adults was highest in chronic renal disease patients (RR=23.6 [19–49 years]; RR=23.7 [≥65 years]), whereas the risk of PP in adults aged between 50 and 64 years was highest in chronic lung disease patients (R=12.8). In the MDV database, the risk of PP was highest in chronic lung disease patients across all age groups compared with healthy adults of the same age (RR=5.6 [19–49 years]; RR=6.8 [50–64 years]; RR=4.9 [≥65 years]).

Compared with healthy adults of the same age, the risk of IPD was highest in adults with cancer aged between 19 and 49 years and 50 and 64 years in the JMDC database (RR=206.6 and 26.5, respectively), whereas the risk of IPD was highest in older adults with chronic renal disease (RR=51.3). In the MDV database, the risk of IPD was highest in young adults with chronic heart disease (RR=18.4), and adults aged between 50 and 64 years and those aged ≥65 years with chronic lung disease (RR=21.4 and 4.7, respectively) compared with healthy adults of the same age.

Across all ages, PP and IPD rates were highest in adults with two or more medical conditions. PP rates in adults with two or more underlying medical conditions were nine to 17 times and three to four times the rate in healthy adults of the same age in the JMDC and

MDV databases, respectively. IPD rates in adults with two or more underlying medical conditions were eight to 42 times and four to 16 times the rates in healthy adults in the JMDC and MDV databases, respectively. The PP rates in immunocompromised adults were 10 to 17 times and two to three times the rate in healthy adults of the same age in the JMDC and MDV databases, while the IPD rates were 15 to 79 times and three to 10 times the rates in healthy adults in the JMDC and MDV databases, respectively.

DISCUSSION

The Japanese Respiratory Society Guidelines for the Management of Community-Acquired Pneumonia in Adults[14] recommend pneumococcal vaccination for individuals aged between 2 and 64 years who have an underlying medical condition. However, little is known about the real-world burden of pneumococcal disease in Japanese adults with these conditions. This retrospective cohort study used two healthcare databases to evaluate the burden of pneumococcal disease in at-risk adults and adults with high-risk medical conditions to close this data gap in Japan.

Similar to previous research,[4,18,25] the principal findings of our study revealed that adults with an underlying medical condition were at increased risk of PP and IPD, compared with adults without these conditions. This was found not only among older adults aged ≥65 years but also among younger adults aged between 19 and 64 years. Our study also showed that the risk of PP and IPD increased with the number of underlying medical conditions in both younger and older adults, supporting the concept of “risk-stacking” demonstrated by previous studies.[3,17,18,29]

We also found some differences in the conditions that place individuals at increased risk of pneumococcal disease between younger and older adults. While the risk of PP and IPD was highest in older adults with chronic renal and lung diseases, the risk of PP and IPD in adults aged between 50 and 64 years was highest among patients with chronic lung disease and cancer. These results are similar to those of a previous study in which adults with chronic obstructive pulmonary disease were found to have the highest risk of IPD.[29]

In adults aged between 50 and 64 years with an underlying medical condition, PP rates in the JMDC database and IPD rates in both the JMDC and MDV databases were higher than the rates in healthy older adults aged ≥65 years, while the same trend was not observed for PP rates in the MDV database. Although pneumococcal vaccination history was not available in the two databases, the pneumococcal vaccination rate was considered low in adults aged ≥65 years during our study period, which ended in 31 December 2014. This is because there was little overlap between our study period and the National Immunization Program in Japan, which has provided a subsidy for PPV23 vaccination for adults aged ≥65 years as of 1 October 2014.[13] The influence of the subsidy for PPV23 vaccination on the PPV23 vaccination rate in adults aged ≥65 years was considered marginal during our study period. Thus, our results imply that adults aged between 50 and 64 years with an underlying medical condition may be at a greater risk of pneumococcal disease compared with healthy adults aged ≥65 years.

The rates of PP and IPD were higher in the MDV than the JMDC database in adults with and without an underlying medical condition across all age subgroups. This may not be surprising given that the two databases are drawn from different adult populations in Japan. Adults in the JMDC database represent a population of younger working adults, while those in the MDV database represent a population in need of healthcare services (i.e., hospitalised patients and outpatients). These differences in background characteristics may explain the variation in risk of PP and IPD between the two databases. Thus, the results from either database alone may not be generalisable to the general population of adults in Japan. Nonetheless, results from both databases support the idea that both younger and older adults with an underlying medical condition in Japan are at increased risk of pneumococcal disease compared with healthy adults of the same age. The findings observed in Japan are consistent with similar studies conducted in the US and Germany.[3,17,18,25]

Limitations

This study had some limitations. Regarding the internal validity, using ICD-10 codes to identify medical conditions and episodes of PP and IPD may lead to misclassification. In addition, PP is often under-coded in claims data. Owing to the limited data availability in the two databases, these analyses did not consider potential confounders other than age and sex, such as pneumococcal vaccination history and residential environment, which might significantly influence the risk of PP and IPD. With regard to external validity, results from only one database cannot be extrapolated to the general population of adults in Japan as subjects in the two databases may be representative of different adult populations.

Conclusion

Adults of all ages with an underlying medical condition, including immunocompetent and immunocompromised adults, are at greater risk of pneumococcal disease, compared with adults without any condition in Japan. This risk increases with the number of underlying medical conditions. Adults aged between 50 and 64 years with an underlying medical condition have a greater risk of pneumococcal disease than adults aged ≥65 years without any condition. Our study findings can help healthcare practitioners and policy makers identify patient groups that are vulnerable to pneumococcal disease and can benefit from pneumococcal vaccination. Adults aged ≥65 years as well as adults aged between 60 and 64 years with a specific medical condition are eligible to receive the subsidy for PPV23 under the National Immunization Program in Japan.[13] However, our results support extending the pneumococcal vaccination to younger adults with an underlying medical condition, especially those aged between 50 and 64 years.

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Disclosure

KI, AS, and SK are employees of MSD K.K., a group of Merck Sharp & Dohme Corp., which is a subsidiary of Merck & Co., Inc. (Kenilworth, NJ, USA). KN and MA received research grants and lecture fees from MSD K.K. TP and MAK are employees of Merck & Co., Inc. Employees may hold stock and/or stock options in the company. The study sponsor, Merck & Co., Inc., and MSD K.K. reviewed the study design; participated in the collection, analysis, and interpretation of the data; critically reviewed the report; and decided to submit the paper for publication.

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Author contributions

KI contributed to the conception or design of the study, and the acquisition, analysis, interpretation of the data, and drafting the manuscript. TP and MAK contributed to interpretation of the data and revision of the paper for important intellectual content. KN and MA contributed to interpretation of data and provided comments from a pulmonologist's point of view. AS contributed to analysis of the data and revision of the paper. SK contributed to the conception and design of the study, the acquisition and interpretation of data, and drafting the manuscript. All authors gave final approval of the version to be published.

Data sharing statement

Data are available on request from the corresponding author.

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Figure legend

Supplementary Figure 1. Study design

Abbreviations: IPD, invasive pneumococcal disease; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PP, pneumococcal pneumonia

Table 1. Rates and rate ratios of pneumococcal pneumonia in the JMDC database

	All ages (≥19 years old[2])		Age subgroups					
			19–49 years old		50–64 years old		≥65 years old[2]	
	Rate[3]	RR[4] (95% CI)	Rate [3]	RR[5] (95% CI)	Rate[3]	RR[5] (95% CI)	Rate[3]	RR[5] (95% CI)
Overall	12.5		8.3		21.6		78.0	
Risk status								
Healthy (no condition)	7.3	1.0	6.3	1.0	11.5	1.0	13.2	1.0
Immunocompetent	55.7	5.3 (4.5–6.2)	33.6	5.4 (4.3–6.6)	59.1	5.0 (4.0–6.4)	180.8	8.2 (4.3–15.5)
Immunocompromised	135.2	12.9 (10.4–16.0)	104.4	17.2 (12.6–23.4)	115.0	10.2 (7.5–13.8)	325.2	16.3 (8.3–32.0)
Medical condition[1]								
No condition	7.3	1.0	6.3	1.0	11.5	1.0	13.2	1.0
Chronic heart disease	93.8	7.1 (5.7–8.8)	78.4	12.5 (8.5–18.3)	68.5	5.6 (4.0–7.8)	206.8	10.1 (5.2–19.7)
Chronic lung disease	92.8	10.8 (9.2–12.6)	51.6	8.2 (6.6–10.4)	143.1	12.8 (9.9–16.6)	356.4	18.8 (9.8–36.3)
Diabetes mellitus	70.1	5.7 (4.8–6.9)	35.9	5.7 (3.9–8.3)	65.9	5.4 (4.1–7.0)	187.9	9.0 (4.7–17.3)
Chronic liver disease	35.9	3.3 (2.6–4.3)	24.3	3.9 (2.6–5.9)	38.6	3.2 (2.2–4.7)	87.5	4.3 (2.0–9.4)
Chronic renal disease	151.6	13.4 (10.1–17.9)	148.2	23.6 (15.6–35.8)	67.8	5.6 (3.0–10.5)	517.2	23.7 (11.3–49.7)
Cancer	128.9	11.2 (9.0–14.1)	72.1	11.5 (7.4–18.0)	137.2	12.5 (9.1–17.1)	261.5	11.9 (5.8–24.1)
Number of conditions								
0	7.3	1.0	6.3	1.0	11.5	1.0	13.2	1.0
1	28.3	3.2 (2.6–3.8)	19.4	3.1 (2.3–4.1)	32.9	2.8 (2.1–3.8)	86.3	3.9 (1.9–8.0)
≥2	129.1	11.6 (9.7–13.9)	108.2	17.4 (13.4–22.6)	104.9	8.9 (6.9–11.6)	272.5	11.9 (6.2–22.8)

(1) Results of subgroups with other medical conditions, including HIV/AIDS, alcoholism, asplenia, organ transplantation, and cerebrospinal fluid leakage, are not shown.
(2) Adults ≥75 years were not included in the JMDC database.
(3) Per 100,000 person-year
(4) Age-and-sex-adjusted rate ratio
(5) Sex-adjusted rate ratio

Abbreviations: CI, confidence interval; JMDC, Japan Medical Data Center; RR, rate ratio

Table 2. Rates and rate ratios of pneumococcal pneumonia in the MDV database

	All ages (≥19 years old)		Age subgroups					
			19–49 years old		50–64 years old		≥65 years old	
	Rate[2]	RR[3] (95% CI)	Rate[2]	RR[4] (95% CI)	Rate[2]	RR[4] (95% CI)	Rate[2]	RR[4] (95% CI)
Overall	100.2		24.9		46.8		150.8	
Risk status								
Healthy (no condition)	55.6	1.0	17.8	1.0	30.2	1.0	93.0	1.0
Immunocompetent	166.1	2.3 (2.1–2.5)	50.9	2.9 (1.9–4.2)	78.4	2.5 (2.0–3.2)	216.6	2.2 (2.0–2.5)
Immunocompromised	135.2	1.8 (1.6–2.0)	48.0	2.7 (1.7–4.4)	54.0	1.7 (1.3–2.3)	177.1	1.8 (1.6–2.0)
Medical condition[1]								
No condition	55.6	1.0	17.8	1.0	30.2	1.0	93.0	1.0
Chronic heart disease	206.0	2.6 (2.3–2.9)	53.2	3.2 (1.7–6.0)	79.2	2.4 (1.8–3.2)	249.0	2.5 (2.3–2.8)
Chronic lung disease	377.4	5.2 (4.7–5.7)	97.8	5.6 (3.6–8.5)	212.1	6.8 (5.2–8.9)	479.2	4.9 (4.4–5.5)
Diabetes mellitus	140.7	1.9 (1.7–2.1)	42.7	2.6 (1.5–4.5)	60.8	1.8 (1.4–2.5)	182.1	1.8 (1.6–2.1)
Chronic liver disease	146.3	2.1 (1.9–2.4)	42.6	2.5 (1.4–4.5)	80.7	2.5 (1.9–3.4)	198.0	2.0 (1.8–2.3)
Chronic renal disease	197.8	2.6 (2.2–3.0)	85.5	5.0 (2.5–10.2)	88.3	2.7 (1.7–4.3)	248.0	2.5 (2.1–2.9)
Cancer	126.1	1.7 (1.5–1.9)	45.1	2.5 (1.5–4.3)	48.3	1.6 (1.2–2.2)	165.5	1.7 (1.5–1.9)
Number of conditions								
0	55.6	1.0	17.8	1.0	30.2	1.0	93.0	1.0
1	86.9	1.3 (1.2–1.5)	31.1	1.7 (1.1–2.7)	41.3	1.3 (1.0–1.8)	122.4	1.3 (1.1–1.4)
≥2	211.4	2.8 (2.5–3.0)	75.4	4.2 (2.6–6.7)	98.2	3.1 (2.4–4.0)	257.9	2.7 (2.4–3.0)

(1) Results of subgroups with other medical conditions, including HIV/AIDS, alcoholism, asplenia, organ transplantation, and cerebrospinal fluid leakage, are not shown.
(2) Per 100,000 person-year
(3) Age-and-sex-adjusted rate ratio
(4) Sex-adjusted rate ratio

Abbreviations: CI, confidence interval; MDV, Medical Data Vision; RR, rate ratio

Table 3. Rates and rate ratios of invasive pneumococcal diseases in the JMDC database

	All ages (≥19 years old[2])		Age subgroups					
			19–49 years old		50–64 years old		≥65 years old[2]	
	Rate[3]	RR[4] (95% CI)	Rate[3]	RR[5] (95%CI)	Rate[3]	RR[5] (95% CI)	Rate[3]	RR[5] (95% CI)
Overall	1.2		0.5		3.3		4.9	
Risk status								
Healthy (no condition)	0.6	1.0	0.3	1.0	1.6	1.0	1.2	1.0
Immunocompetent	5.4	5.3 (3.2–8.8)	1.4	4.6 (1.7–12.7)	9.3	5.7 (3.1–10.6)	11.1	4.3 (0.4–41.3)
Immunocompromised	24.6	29.7 (16.9–2.1)	20.0	79.0 (34.4–182)	28.7	18.2 (9.2–36.1)	22.7	14.9 (1.6–143)
Medical condition[1]								
No condition	0.6	1.0	0.3	1.0	1.6	1.0	1.2	1.0
Chronic heart disease	16.4	15.7 (8.8–28.0)	10.8	33.6 (11.1–102)	20.0	11.2 (5.5–22.8)	14.4	10.8 (1.1–104)
Chronic lung disease	6.8	16.4 (9.0–30.2)	0.0	0	19.7	12.9 (6.4–25.8)	26.4	5.1 (0.4–63.4)
Diabetes mellitus	12.2	12.6 (7.4–21.2)	4.8	14.7 (4.8–44.3)	16.3	10.3 (5.5–19.5)	13.7	2.8 (0.2–33.3)
Chronic liver disease	11.0	13.0 (7.5–22.7)	1.0	4.1 (0.5–31.9)	20.4	11.9 (6.2–22.9)	17.5	13.3 (1.4–128)
Chronic renal disease	16.5	25.2 (10.3–61.8)	12.4	120.7 (25.0–583)	6.2	4.2 (0.6–31.5)	77.6	51.3 (5.3–493)
Cancer	28.8	43.3 (24.7–76.2)	24.0	206.6 (80.6–530)	39.2	26.5 (13.4–525)	0.0	0
Number of conditions								
0	0.6	1.0	0.3	1.0	1.6	1.0	1.2	1.0
1	2.2	3.6 (1.8–7.1)	1.3	5.3 (1.7–16.2)	3.9	2.4 (1.0–5.5)	0.0	0
≥2	18.3	18.7 (10.9–32.1)	14.1	42.2 (18.5–96.6)	19.8	11.9 (6.2–22.8)	22.7	8.2 (0.9–79.2)

(1) Results of subgroups with other medical conditions, including HIV/AIDS, alcoholism, asplenia, organ transplantation, and cerebrospinal fluid leakage, are not shown.
(2) Adults ≥75 years were not included in the JMDC database.
(3) Per 100,000 person-year
(4) Age-and-sex-adjusted rate ratio
(5) Sex-adjusted rate ratio

Abbreviations: CI, confidence interval; JMDC, Japan Medical Data Center; RR, rate ratio

Table 4. Rates and rate ratios of invasive pneumococcal disease in the MDV database

	All ages (≥19 years old)		Age subgroups					
			19–49 years old		50–64 years old		≥65 years old	
	Rate[2]	RR[3] (95% CI)	Rate[2]	RR[4] (95% CI)	Rate[2]	RR[4] (95% CI)	Rate[1]	RR[4] (95% CI)
Overall	4.6		1.5		3.8		5.9	
Risk status								
Healthy (no condition)	1.9	1.0	0.9	1.0	0.9	1.0	3.0	1.0
Immunocompetent	8.0	3.8 (2.4–6.2)	4.0	4.0 (0.9–18.4)	7.7	9.2 (2.7–31.2)	8.7	3.0 (1.7–5.1)
Immunocompromised	8.6	4.0 (2.4–6.7)	4.2	4.7 (0.8–28.1)	8.6	9.8 (2.8–34.7)	9.2	3.1 (1.7–5.6)
Medical condition[1]								
No condition	1.9	1.0	0.9	1.0	0.9	1.0	3.0	1.0
Chronic heart disease	9.3	4.7 (2.8–7.9)	17.7	18.4 (4.0–84.2)	6.4	8.0 (2.0–32.0)	9.6	3.3 (1.8–5.8)
Chronic lung disease	13.8	7.1 (4.2–12.0)	5.9	6.5 (1.1–39.0)	18.4	21.4 (5.9–77.8)	13.8	4.7 (2.5–8.7)
Diabetes mellitus	8.5	4.4 (2.6–7.3)	10.7	11.0 (2.4–50.6)	8.5	10.4 (2.9–37.2)	8.3	2.8 (1.6–5.2)
Chronic liver disease	8.9	4.7 (2.7–8.2)	5.7	5.9 (1.0–36.1)	5.8	6.9 (1.6–28.9)	11.1	3.8 (2.0–7.2)
Chronic renal disease	9.1	4.7 (2.2–10.0)	0	0	12.6	15.4 (3.1–76.8)	9.3	3.2 (1.3–7.7)
Cancer	8.6	4.4 (2.6–7.4)	5.3	6.0 (1.0–36.2)	7.6	8.6 (2.3–31.9)	9.3	3.2 (1.8–5.9)
Number of conditions								
0	1.9	1.0	0.9	1.0	0.9	1.0	3.0	1.0
1	3.1	1.6 (0.9–2.8)	0	0	2.8	3.3 (0.8–13.8)	4.0	1.4 (0.7–2.7)
≥2	12.1	5.8 (3.6–9.5)	11.6	11.6 (2.5–54.0)	12.9	16.2 (4.7–55.7)	11.9	4.1 (2.3–7.1)

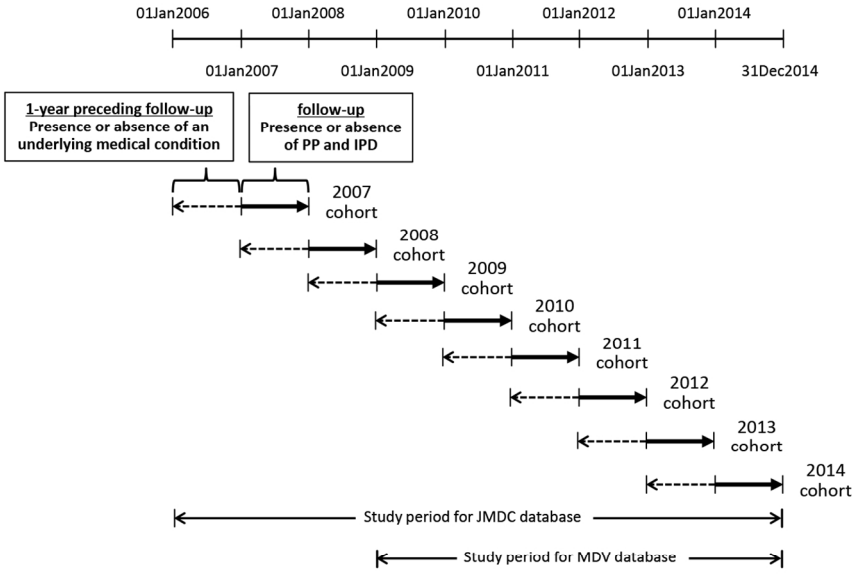
(1) Results of subgroups with other medical conditions, including HIV/AIDS, alcoholism, asplenia, organ transplantation, and cerebrospinal fluid leakage, are not shown.
(2) Per 100,000 person-year
(3) Age-and-sex-adjusted rate ratio
(4) Sex-adjusted rate ratio
Abbreviations: CI, confidence interval; MDV, Medical Data Vision; RR, rate ratio

Supplementary Table 1. Characteristics of study subjects from the JMDC and MDV database

	JMDC					MDV				
	Cumulative number of adults	Person-years [1]		PP Events	IPD Events	Cumulative number of adults	Person-years [1]		PP Events	IPD Events
			%					%		
Overall	7,433,221	6,721,329	100%	840	80	2,967,475	2,565,033	100%	2,569	117
Age										
19–49 years old	5,744,222	5,211,057	78%	433	28	566,908	478,300	18%	117	7
50–64 years old	1,522,054	1,368,055	20%	296	45	776,809	672,365	26%	318	26
≥65 years old [2]	166,945	142,218	2%	111	7	1,623,758	1,415,368	55%	2,134	84
Sex										
Female	3,326,903	2,957,528	44%	327	20	1,620,634	1,394,668	54%	1,109	61
Male	4,106,318	3,763,802	56%	513	60	1,346,841	1,170,364	46%	1,460	56
Risk status										
Healthy (no condition)	6,603,349	5,975,767	89%	436	33	1,494,204	1,242,491	48%	691	23
Immunocompetent	758,769	681,915	10%	380	37	1,151,533	1,033,332	40%	1,725	83
Immunocompromised	128,966	113,909	2%	154	28	628,565	556,208	22%	752	48
Medical conditions										
No condition	6,603,349	5,975,767	89%	436	33	1,494,204	1,242,491	48%	691	23
Chronic heart disease	144,228	127,884	2%	120	21	522,688	471,870	18%	972	44
Chronic lung disease	313,269	281,336	4%	261	19	299,695	268,656	10%	1,014	37
Diabetes mellitus	283,483	253,904	4%	178	31	594,890	541,680	21%	761	46
Chronic liver disease	232,397	208,938	3%	75	23	334,107	302,832	12%	443	27
Chronic renal disease	40,585	36,286	0.5%	55	6	122,872	109,707	4%	217	10
Cancer	91,004	79,882	1%	103	23	529,116	466,966	18%	589	40
HIV/AIDS	NR	NR	NR	NR	NR	521	480	0.02%	1	0
Alcoholism	2,366	2,078	0.03%	1	0	2,744	2,421	0.09%	4	0
Asplenia	1,732	1,538	0.02%	30	16	6,799	6,031	0.2%	26	1
Organ transplantation	2,525	2,214	0.03%	17	16	3,895	3,535	0.1%	21	2
Cerebrospinal fluid leakage	298	264	0.004%	0	0	355	318	0.01%	0	0
Number of conditions										
0	6,603,349	5,975,767	89%	436	33	1,494,204	1,242,491	48%	691	23
1	614,013	554,305	8%	157	12	824,413	736,812	29%	640	23
≥2	215,859	191,257	3%	247	35	648,858	585,730	23%	1,238	71

(1) Per 100,000 person-years, (2) Adults ≥75 years were not included in the JMDC database. Abbreviations: IPD, invasive pneumococcal disease; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; NR, not recorded; PP, pneumococcal pneumonia

Supplementary Figure 1.



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Appendix 1. International Classification of Diseases, version 10 Codes

Condition	ICD-10 codes (2015)	Description	Disease code defined by MHLW Japan	Description	ICD-10 codes (2015)	Description	Disease code defined by MHLW Japan	Description
Chronic heart disease	I05	Rheumatic mitral valve diseases						
	I06	Rheumatic aortic valve diseases						
	I07	Rheumatic tricuspid valve diseases						
	I08	Multiple valve diseases						
	I09	Other rheumatic heart diseases						
	I11.0	Hypertensive heart disease with (congestive) heart failure						
	I13.0	Hypertensive heart and renal disease with (congestive) heart failure						
	I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure						
	I20	Angina pectoris						
	I21	Acute myocardial infarction						
	I22	Subsequent myocardial infarction						
	I23	Certain current complications following acute myocardial infarction						
	I24	Other acute ischaemic heart diseases						
	I25	Chronic ischemic heart disease						
	I25.1	Atherosclerotic heart disease						
	I25.2	Old myocardial infarction						
	I25.3	Aneurysm of heart						
	I25.4	Coronary artery aneurysm and dissection						
	I25.5	Ischemic cardiomyopathy						
	I25.6	Silent myocardial ischemia						
	I25.8	Other forms of chronic ischemic heart disease						
	I25.9	Chronic ischemic heart disease, unspecified						
	I27	Other pulmonary heart diseases						
	I34	Nonrheumatic mitral valve disorders						
	I35	Nonrheumatic aortic valve disorders						
	I37	Pulmonary valve disorders						
	I38	Endocarditis, valve unspecified						

	I42	Cardiomyopathy
	I43	Cardiomyopathy in diseases classified elsewhere
	I50	Heart failure
	I51	Complications and ill-defined descriptions of heart disease
	Q20	Congenital malformations of cardiac chambers and connections
	Q21	Congenital malformations of cardiac septa
	Q22	Congenital malformations of pulmonary and tricuspid valves
	Q23	Congenital malformations of aortic and mitral valves
	Q24	Other congenital malformations of heart
Chronic lung disease	J40	Bronchitis, not specified as acute or chronic
	J41	Simple and mucopurulent chronic bronchitis
	J42	Unspecified chronic bronchitis
	J43	Emphysema
	J44	Other chronic obstructive pulmonary disease
	J45	Asthma
	J46	Status asthmaticus
	J47	Bronchiectasis
	J60	Coalworker pneumoconiosis
	J61	Pneumoconiosis due to asbestos and other mineral fibres
	J62	Pneumoconiosis due to dust containing silica
	J63	Pneumoconiosis due to other inorganic dusts
	J64	Unspecified pneumoconiosis
	J66	Airway disease due to specific organic dust
	J67	Hypersensitivity pneumonitis due to organic dust
	J84	Other interstitial pulmonary diseases
	J96.1	Chronic respiratory failure
	J98	Other respiratory disorders
	E84	Cystic fibrosis
	I27.9	Pulmonary heart disease, unspecified
Diabetes mellitus	E10	Type 1 diabetes mellitus
	E11	Type 2 diabetes mellitus
	E12	Malnutrition-related diabetes mellitus

	E13	Other specified diabetes mellitus
	E14	Unspecified diabetes mellitus
Chronic liver disease	B16 (except B16.9)	Acute hepatitis B (except Acute hepatitis B without delta-agent and without hepatic coma)
	B17 (except B17.1)	Other acute viral hepatitis (except Acute hepatitis C)
	B18	Chronic viral hepatitis
	B19 (except B19.9)	Unspecified viral hepatitis (except Unspecified viral hepatitis without hepatic coma)
	K70	Alcoholic liver disease
	K71 (except K71.2)	Toxic liver disease (exceptToxic liver disease with hepatic necrosis)
	K72 (except K72.0)	Hepatic failure, not elsewhere classified (except Acute and subacute hepatic failure)
	K73	Chronic hepatitis, not elsewhere classified
	K74	Fibrosis and cirrhosis of liver
	K75	Other inflammatory liver diseases
	K76	Other diseases of liver
	K77	Liver disorders in diseases classified elsewhere
Asplenia	D56	Thalassaemia
	D57	Sickle-cell disorders
	D60	Acquired pure red cell aplasia [erythroblastopenia]
	D61	Other aplastic anaemias
	D73.0	Hyposplenism
	D73.1	Hypersplenism
	D73.8	Other diseases of spleen
	Q89.0	Congenital malformations of spleen
	Q89.3	Situs inversus
Alcoholism	F10.2	Dependence syndrome
HIV infection	B20	Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases
	B21	Human immunodeficiency virus [HIV]

		disease resulting in malignant neoplasms
	B22	Human immunodeficiency virus [HIV] disease resulting in other specified diseases
	B23	Human immunodeficiency virus [HIV] disease resulting in other conditions
	B24	Unspecified human immunodeficiency virus [HIV] disease
Cancer	C00	Malignant neoplasm of lip
	C01	Malignant neoplasm of base of tongue
	C02	Malignant neoplasm of other and unspecified parts of tongue
	C03	Malignant neoplasm of gum
	C04	Malignant neoplasm of floor of mouth
	C05	Malignant neoplasm of palate
	C06	Malignant neoplasm of other and unspecified parts of mouth
	C07	Malignant neoplasm of parotid gland
	C08	Malignant neoplasm of other and unspecified major salivary glands
	C09	Malignant neoplasm of tonsil
	C10	Malignant neoplasm of oropharynx
	C11	Malignant neoplasm of nasopharynx
	C12	Malignant neoplasm of piriform sinus
	C13	Malignant neoplasm of hypopharynx
	C14	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
	C15	Malignant neoplasm of oesophagus
	C16	Malignant neoplasm of stomach
	C17	Malignant neoplasm of small intestine
	C18	Malignant neoplasm of colon
	C19	Malignant neoplasm of rectosigmoid junction
	C20	Malignant neoplasm of rectum
	C21	Malignant neoplasm of anus and anal canal
	C22	Malignant neoplasm of liver and intrahepatic bile ducts
	C23	Malignant neoplasm of gallbladder
	C24	Malignant neoplasm of other and unspecified parts of biliary tract
	C25	Malignant neoplasm of pancreas
	C26	Malignant neoplasm of other and ill-defined

	digestive organs
C30	Malignant neoplasm of nasal cavity and middle ear
C31	Malignant neoplasm of accessory sinuses
C32	Malignant neoplasm of larynx
C33	Malignant neoplasm of trachea
C34	Malignant neoplasm of bronchus and lung
C37	Malignant neoplasm of thymus
C38	Malignant neoplasm of heart, mediastinum and pleura
C39	Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs
C40	Malignant neoplasm of bone and articular cartilage of limbs
C41	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C43	Malignant melanoma of skin
C44	Other malignant neoplasms of skin
C45	Mesothelioma
C46	Kaposi sarcoma
C47	Malignant neoplasm of peripheral nerves and autonomic nervous system
C48	Malignant neoplasm of retroperitoneum and peritoneum
C49	Malignant neoplasm of other connective and soft tissue
C50	Malignant neoplasm of breast
C51	Malignant neoplasm of vulva
C52	Malignant neoplasm of vagina
C53	Malignant neoplasm of cervix uteri
C54	Malignant neoplasm of corpus uteri
C55	Malignant neoplasm of uterus, part unspecified
C56	Malignant neoplasm of ovary
C57	Malignant neoplasm of other and unspecified female genital organs
C58	Malignant neoplasm of placenta
C60	Malignant neoplasm of penis
C61	Malignant neoplasm of prostate

C62	Malignant neoplasm of testis
C63	Malignant neoplasm of other and unspecified male genital organs
C64	Malignant neoplasm of kidney, except renal pelvis
C65	Malignant neoplasm of renal pelvis
C66	Malignant neoplasm of ureter
C67	Malignant neoplasm of bladder
C68	Malignant neoplasm of other and unspecified urinary organs
C69	Malignant neoplasm of eye and adnexa
C70	Malignant neoplasm of meninges
C71	Malignant neoplasm of brain
C72	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
C73	Malignant neoplasm of thyroid gland
C74	Malignant neoplasm of adrenal gland
C75	Malignant neoplasm of other endocrine glands and related structures
C76	Malignant neoplasm of other and ill-defined sites
C77	Secondary and unspecified malignant neoplasm of lymph nodes
C78	Secondary malignant neoplasm of respiratory and digestive organs
C79	Secondary malignant neoplasm of other and unspecified sites
C80	Malignant neoplasm, without specification of site
C81	Hodgkin lymphoma
C82	Follicular lymphoma
C83	Non-follicular lymphoma
C84	Mature T/NK-cell lymphomas
C85	Other and unspecified types of non-Hodgkin lymphoma
C86	Other specified types of T/NK-cell lymphoma
C88	Malignant immunoproliferative diseases
C90	Multiple myeloma and malignant plasma cell neoplasms

	C91	Lymphoid leukaemia		
	C92	Myeloid leukaemia		
	C93	Monocytic leukaemia		
	C94	Other leukaemias of specified cell type		
	C95	Leukaemia of unspecified cell type		
	C96	Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissue		
	C97	Malignant neoplasms of independent (primary) multiple sites		
Chronic renal disease	I12	Hypertensive renal disease		
	I13	Hypertensive heart and renal disease		
	N03	Chronic nephritic syndrome		
	N04	Nephrotic syndrome		
	N05	Unspecified nephritic syndrome		
	N08	Glomerular disorders in diseases classified elsewhere		
	N18	Chronic kidney disease		
	N19	Unspecified kidney failure		
	Q60	Renal agenesis and other reduction defects of kidney		
	Q61	Cystic kidney disease		
	Q62	Congenital obstructive defects of renal pelvis and congenital malformations of ureter		
	Q63	Other congenital malformations of kidney		
	Q64	Other congenital malformations of urinary system		
	Z94.0	Kidney transplant status		
	T80.9	Unspecified complication following infusion, transfusion and therapeutic injection	9999004	Renal dialysis complication
	T80.9	Unspecified complication following infusion, transfusion and therapeutic injection	8842133	Dialysis disequilibrium syndrome
	T80.9	Unspecified complication following infusion, transfusion and therapeutic injection	8842134	Dialysis hypotension
	T80.9	Unspecified complication following infusion, transfusion and therapeutic injection	8842132	Dialysis difficulty
	T82.7	Infection and inflammatory reaction due to other cardiac and vascular devices, implants	8845140	Dialysis shunt infection

		and grafts		
	T82.5	Mechanical complication of other cardiac and vascular devices and implants	8845141	Dialysis shunt failure
	T82.7	Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts	8847235	Dialysis shunt virtual aneurysm
	T82.8	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts	8844085	Dialysis shunt stenosis
	T82.8	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts	8844087	Dialysis shunt arteriovenous aneurysm
	T82.8	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts	8844088	Dialysis shunt obstruction
	T82.8	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts	8844086	Dialysis shunt venous hypertension
Organ transplantation	T86	Complications of transplanted organs and tissue		
	Z94	Transplanted organ and tissue status		
Cerebrospinal fluid leakage	S06.8	Other intracranial injuries	3498002	Traumatic cerebrospinal fluid otorrhoea
	S06.8	Other intracranial injuries	3498003	Traumatic cerebrospinal fluid rhinorrhoea
	G96.0	Cerebrospinal fluid leak	3498007	Spinal leakage
	G96.0	Cerebrospinal fluid leak	8847107	Cerebrospinal fluid otorrhoea
	S06.8	Other intracranial injuries	8843154	Open traumatic cerebrospinal fluid otorrhoea
	S06.8	Other intracranial injuries	8843155	Open traumatic cerebrospinal fluid rhinorrhoea
	S06.8	Other intracranial injuries	8843261	Traumatic cerebrospinal fluid otorrhoea
	S06.8	Other intracranial injuries	8843262	Traumatic

	S06.8	Other intracranial injuries	8843259	cerebrospinal fluid rhinorrhoea					
	S06.8	Other intracranial injuries	8843260	Traumatic cerebrospinal fluid otorrhoea					
	S06.8	Other intracranial injuries	8843531	Traumatic cerebrospinal fluid rhinorrhoea					
	S06.8	Other intracranial injuries	8843532	Closed traumatic cerebrospinal fluid otorrhoea					
	G96.0	Cerebrospinal fluid leak	3498021	Closed traumatic cerebrospinal rhinorrhoea					
	G96.0	Cerebrospinal fluid leak	8847240	Spinal leakage					
	G97.0	Cerebrospinal fluid leak from spinal puncture	8836019	Cerebrospinal fluid leakage					
Invasive pneumococcal disease	A49.1	Streptococcal infection, unspecified site	8847765	Cerebrospinal fluid leak from spinal puncture					
	G00.1	Pneumococcal meningitis	3201001	Invasive pneumococcal infection					
	A40.3	Sepsis due to Streptococcus pneumoniae	8838800	Pneumococcal meningitis					
	A49.9	Bacterial infection, unspecified	7907001	Pneumococcal sepsis					
	A41.9	Sepsis, unspecified	0389004	Bacteraemia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	G04.2	Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified	8831417	Sepsis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	G03.9	Meningitis, unspecified	3229007	Purulent cerebral meningitis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	G04.9	Encephalitis, myelitis and encephalomyelitis,	3239028	Meningitis	and	A49.1	Streptococcal	8847809	Pneumococcal

		unspecified					infection, unspecified site		infection
	I33.0	Acute and subacute infective endocarditis	8838820	Septic endocarditis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	I30.1	Infective pericarditis	8838821	Septic pericarditis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	J20.9	Acute bronchitis, unspecified	8838818	Septic bronchitis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	J18.9	Pneumonia, unspecified	8838823	Septic pneumonia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	A49.9	Bacterial infection, unspecified	0389014	Transient bacteraemia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	A49.9	Bacterial infection, unspecified	0389015	Intermittent bacteraemia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	A49.9	Bacterial infection, unspecified	0389016	Persistent bacteraemia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	A49.9	Bacterial infection, unspecified	7907001	Bacteraemia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	A41.9	Sepsis, unspecified organism			and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	M86.9	Osteomyelitis, unspecified	8838819	Septic osteomyelitis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	A41.8	Other specified sepsis	8847009	Gram-positive bacterial sepsis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
Pneumococcal pneumonia	J13	Pneumonia due to Streptococcus pneumoniae	8838802	Pneumococcal pneumonia					
	J20.2	Acute bronchitis due to streptococcus	8838798	Pneumococcal bronchitis					
	J15.9	Bacterial pneumonia, unspecified	4829003	Bacterial pneumonia	and	A49.1	Streptococcal	8847809	Pneumococcal

								infection, unspecified site	infection
	J18	Pneumonia, organism unspecified	8832171	Bronchopneumonia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	J18	Pneumonia, organism unspecified	4860030	Pneumonia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	J86	Pyothorax			and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	J90	Pleural effusion, not elsewhere classified			and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	J91	Pleural effusion in other conditions classified elsewhere			and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
Exclusion criteria (below)									
	A49.9	Bacterial infection, unspecified	7907001	Bacteraemia					
	A49.9	Bacterial infection, unspecified	0389014	Transient bacteraemia					
	A49.9	Bacterial infection, unspecified	0389015	Intermittent bacteraemia					
	A49.9	Bacterial infection, unspecified	0389016	Persistent bacteraemia					
	A41.9	Sepsis, unspecified organism							
	A41.8	Other specified sepsis	8847009	Gram-positive bacterial sepsis					

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Reported on page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1 Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2 Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P4-P5
Objectives	3	State specific objectives, including any prespecified hypotheses	P5, L17-22
Methods			
Study design	4	Present key elements of study design early in the paper	P2-P5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P5-P8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	P6 Study design and population
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	P6 Study design and population
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P6-P7 Study variables
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P5 Data source
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	P6 Study design and population
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6-P7 Study variables
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P7-P8 Statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	P7 Study variables
		(*d*) If applicable, explain how loss to follow-up was addressed	P7 Study variables
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P8 Characteristics of the study population
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	P8 Characteristics

		confounders	of the study population
		(b) Indicate number of participants with missing data for each variable of interest	P8 Characteristics of the study population
		(c) Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures over time	P8-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P8-10
		(*b*) Report category boundaries when continuous variables were categorized	P8-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P8-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	P10 Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P11-12 Limitation
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	P12 conclusion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P13 Funding

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Risk of pneumococcal diseases in adults with underlying medical conditions: a retrospective, cohort study using two Japanese healthcare databases

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Risk of pneumococcal diseases in adults with underlying medical conditions: a retrospective, cohort study using two Japanese healthcare databases

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ABSTRACT

Objectives: To quantify the risk of pneumococcal pneumonia (PP) and invasive pneumococcal disease (IPD) in adults aged ≥19 years with underlying medical conditions compared with healthy adults of the same age in Japan.

Design: An observational, retrospective, cohort study using two healthcare claims databases in Japan: Japan Medical Data Center (JMDC) and Medical Data Vision (MDV) databases.

Participants: A total of 10.4 million individuals, representing 9.3 million person-years of follow-up, were included in the analysis. Eleven medical conditions as well as PP and IPD were identified by ICD-10 diagnostic codes and/or local disease codes used in Japan.

Primary outcome measures: Adjusted rate ratios (RRs) for PP and IPD in adults with a medical condition vs. adults without any medical condition were calculated using multivariate Poisson regression models with age and/or sex as covariates.

Results: In the JMDC and MDV databases, respectively, adults ≥19 years with a medical condition (RRs for PP: 3.3 to 13.4, 1.7 to 5.2; RRs for IPD: 12.6 to 43.3, 4.4 to 7.1), adults with two or more medical conditions (PP: 11.6, 2.8; IPD: 18.7, 5.8), and immunocompromised adults (PP: 12.9, 1.8; IPD: 29.7, 4.0) were at greater risk of PP and IPD compared with their healthy counterparts. Adults aged between 50 and 64 years with an underlying medical condition (PP rate: 38.6 to 212.1 per 100,000 person-years) had a higher rate of PP than those aged ≥65 years without any condition (PP rate: 13.2 to 93.0 per 100,000 person-years).

Conclusions: Adults of all ages with an underlying medical condition are at greater risk of PP and IPD compared with adults without any medical condition. This risk increases with the number of underlying medical conditions. Our results support extending pneumococcal vaccination to younger adults with an underlying medical condition, especially those aged between 50 and 64 years.

Keywords: pneumococcal pneumonia, invasive, pneumococcal disease, chronic medical condition

Article summary

- **Strengths and limitations of this study:** Given the well-known differences in the genetic makeup of the Japanese population, data specific to Japan are important to formulate a national immunisation strategy and to protect vulnerable populations.
- Our study results may contribute to further knowledge on the risk of pneumococcal disease in Japanese individuals aged 19 years and older with an underlying medical condition.
- As this study was a retrospective analysis based on insurance claims data, the coding of medical conditions and episodes of pneumococcal pneumonia and invasive pneumococcal disease by ICD-10 codes may lead to misclassification, and pneumococcal pneumonia may be under-coded.
- These analyses did not consider potential confounders other than age and sex, such as pneumococcal vaccination history and residential environment, which might significantly influence the risk of pneumococcal pneumonia and invasive pneumococcal disease.
- Results from only one database cannot be extrapolated to the general population of adults in Japan, and subjects in the two databases may be representative of different adult populations.

INTRODUCTION

Pneumococcal disease, caused by encapsulated *Streptococcus pneumoniae*, is a major cause of community-acquired pneumonia, meningitis, septicaemia, osteomyelitis, septic arthritis, and bacteraemia worldwide. Older adults and children, as well as immunosuppressed individuals, such as those with HIV, are susceptible to pneumococcal disease.[1,2] In addition, adults with certain chronic medical conditions, such as diabetes, chronic lung disease, and chronic heart disease, are also at increased risk of pneumococcal disease.[3,4] These high-risk groups have been targeted for pneumococcal vaccination to reduce the burden of pneumococcal disease in many countries, including the US, Canada, the UK, and Germany.[5-8]

The 23-valent pneumococcal polysaccharide vaccine (PPV23) was licensed in 1988 in Japan, and studies have revealed the protective effects of PPV23 against invasive pneumococcal disease (IPD) and pneumococcal pneumonia (PP).[9-12] Since 2014,[13] the National Immunization Program in Japan has implemented the use of PPV23 for adults aged between 60 and 64 years with underlying medical conditions, in addition to adults aged ≥65 years. Since 2007,[14,15] the Japanese Respiratory Society has advocated an expansion of the program to individuals aged between 2 and 64 years with chronic or immunosuppressive conditions.

Several studies have been conducted in the US and Germany to examine the burden of pneumococcal disease in persons with underlying medical conditions.[16,17] A retrospective analysis of three healthcare claims repositories in the US showed that PP and IPD rates were approximately three times higher in immunocompetent adults with one or more chronic conditions (“at-risk” adults) compared with age-matched healthy adults. Additionally, these rates were approximately four to seven times and four to 10 times higher in adults who were immunocompromised or receiving immunosuppressive therapy (“high-risk” adults), respectively, compared with age-matched healthy adults.[4] A separate study using the same databases demonstrated that associated healthcare costs for IPD were approximately three

to four times and five to 10 times higher in at-risk adults and high-risk adults, respectively, compared with age-matched healthy counterparts.[18]

The risk of pneumococcal disease in individuals with underlying medical conditions is not well characterised in Japan. As differences in the genetic makeup of the Japanese population may lead to different risk patterns of pneumococcal disease compared with other countries, information specific to Japan is important not only for healthcare professionals to identify patients at increased risk of pneumococcal disease, but also for policy makers to formulate a national immunisation strategy to protect vulnerable populations. Therefore, the objective of this study was to quantify the burden of pneumococcal disease in adults aged 19 years and older with an underlying medical condition in Japan.

METHODS

Data source

Two healthcare claims databases, the Japan Medical Data Center (JMDC) database and the Medical Data Vision Company (MDV) database, were used in our study. The JMDC database contains claims data from the Japanese union-managed health insurance system, comprising 10 insurance societies since 2005. The JMDC database includes workers (mostly aged <65 years) employed by mid- to large-sized companies and their dependents, and excludes individuals aged ≥75 years. It has records of more than 3 million individuals.[19] The MDV database contains health insurance claims, administrative data, and laboratory values stored in the electronic records of 16 secondary hospitals with an average of 300 beds, which represented 9% of acute care hospitals in Japan. This database contains records for 7.4 million individuals who received healthcare services at these hospitals since 2003.[20,21] Subjects in the MDV database can be lost to follow-up. Both databases have been used in multiple studies published in peer-reviewed journals.[22-24]

Study design and population

This was an observational, retrospective, cohort study. The study design was based on those of the studies by Shea et al (2014)[4] and Weycker et al (2016)[18] conducted in the US, and that by Pelton et al (2014) conducted in Germany.[25] The study period spanned from 1 January 2006 to 31 December 2014 for the JMDC database and from 1 January 2009 to 31 December 2014 for the MDV database. Adults were included in each yearly cohort if they were aged ≥19 years on the first day of the calendar year and were continuously enrolled over the period from 1 year before to 1 year after 1 January of the calendar years 2007 to 2014 for the JMDC database and 2009 to 2014 for the MDV database. There were no exclusion criteria in this study.

Adults were classified as healthy or having an underlying medical condition based on whether they had the medical conditions of interest during the year preceding 1 January of each calendar year included in the study. If a patient had multiple conditions of interest in the previous year, the patient was assigned to all diagnosed conditions. Subjects without evidence of these conditions were classified as healthy. For each yearly cohort, episodes of pneumococcal disease were identified during the 1-year period from 1 January to 31 December. Multiple yearly cohorts were identified at the beginning of each calendar year during the study period. Subjects who met the inclusion criteria in multiple calendar years were included in corresponding yearly cohorts. The study design is summarised in Supplementary Figure 1.

Study variables

According to guidelines and recommendations in the US, England, and Japan,[7,13,14,26] this study included 11 medical conditions of interest: chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, chronic renal disease, cancer, HIV/AIDS, functional or anatomic asplenia, organ transplantation, alcoholism, and cerebrospinal fluid leakage. At-risk conditions included chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, and alcoholism. High-risk conditions included chronic renal disease, cancer, HIV/AIDS, functional or anatomic asplenia, organ transplantation, and

cerebrospinal fluid leakage.[27] Medical conditions were identified by the International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10) diagnostic codes and/or local disease codes as defined by the Ministry of Health, Labour and Welfare (MHLW) in Japan.[28] Detailed definitions of each medical condition are described in Supplementary Table 1.

Adults were classified as healthy or having an underlying medical condition based on whether they had the medical conditions of interest during the 1-year period preceding follow-up. Adults were classified as having a confirmed medical condition if at least two ICD-10 codes for the condition were recorded in the preceding calendar year. If a patient had multiple conditions of interest in the 1-year period preceding follow-up, the patient was assigned to all diagnosed conditions. Adults without evidence of these conditions were classified as healthy. In addition, adults were classified by the number of medical conditions of interest (0, 1, and 2+ conditions), risk status (healthy, immunocompetent with at-risk conditions, and immunocompromised with high-risk conditions), age (19–49, 50–64, and ≥65 years), and sex (male, female), based on the recommendations for pneumococcal vaccination by the MHLW in Japan,[13] and the recommending bodies in other countries, including the US,[5,27] England,[7] and Germany.[8] Patients with multiple chronic medical conditions were included in all applicable chronic medical condition cohorts. For example, a patient with diabetes mellitus and heart disease in 2007 was included in both the diabetes cohort and the heart disease cohort. This patient, if coded only for heart disease in 2008 (without being coded for diabetes mellitus), was not counted in the diabetes cohort, and thus was counted only in the heart disease cohort of 2008.

Episodes of PP and IPD were identified by the ICD-10 diagnostic codes and/or local disease codes defined by the MHLW in Japan[28] in each calendar year. Episodes were considered distinct if they were separated by an interval of 90 days.[4] PP was defined according to the code of pneumococcal pneumonia alone, the code of pneumococcal bronchitis alone, combined codes of pneumonia and pneumococcal infection at the same day, or other codes. IPD was defined according to the code of invasive pneumococcal

disease, pneumococcal sepsis, pneumococcal meningitis, or others. Detailed definitions of PP and IPD are described in Supplementary Table 1.

Statistical analysis

PP and IPD rates per 100,000 person-years were calculated for the overall sample and by age, sex, medical condition, number of medical conditions, and risk status. Unadjusted rate ratios (RRs) of PP and IPD in adults with and without a medical condition were calculated by comparing the rates of PP and IPD between adults with and those without a medical condition. Multivariate Poisson regression models, with age and/or sex as covariates, were used to determine age-and-sex-adjusted or sex-adjusted RRs of PP and IPD. Analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC, US).

Ethical statement

This study was approved by the ethics committee of Kameda Medical Center, Chiba, Japan, in October 2015, before the initiation of this study.

RESULTS

Characteristics of the study population

A total of 10.4 million individuals, representing 9.3 million person-years of follow-up, were included in the analysis (comprising 6.7 million person-years from the JMDC databases and 2.6 million person-years from the MDV database). In the JMDC database, 78% of adults were aged between 19 and 49 years, 20% were aged between 50 and 64 years, 2% were aged ≥65 years, and the mean age was 39.6 years. Further, 56% were men, 89% had no medical condition, 3% had two or more conditions, 10% were immunocompetent with at-risk conditions, and 3% were immunocompromised with high-risk conditions. In the MDV database, 18% of adults were aged between 19 and 49 years, 26% were aged between 50 and 64 years, 55% were aged ≥65 years, and the mean age was 62.0 years. Further, 46% were men, and 48% had no medical condition, 23% had two or

more conditions, 40% were immunocompetent with at-risk conditions, and 22% were immunocompromised with high-risk conditions. Few study subjects with HIV/AIDS, alcoholism, asplenia, organ transplantation, and cerebrospinal fluid leakage were identified in both databases. Characteristics of the study subjects from the JMDC and MDV databases are shown in Table 1.

The burden of pneumococcal pneumonia and invasive pneumococcal disease

Rates and RRs for PP are shown in Table 2 for the JMDC database and in Table 3 for the MDV database. Rates and RRs for IPD are shown in Table 4 for the JMDC database and in Table 5 for the MDV database.

In both databases, PP and IPD rates increased with age. In the JMDC database, the rate of PP increased from 8.3 per 100,000 person-years in adults aged between 19 and 49 years to 21.6 and 78.0 per 100,000 person-years in adults aged between 50 and 64 years and those aged ≥65 years, respectively. The rate of IPD increased from 0.5 per 100,000 person-years in adults aged between 19 and 49 years to 3.3 and 4.9 per 100,000 person-years in adults aged between 50 and 64 years and ≥65 years, respectively. In the MDV database, the rate of PP increased from 24.9 per 100,000 person-years to 46.8 and 150.8 per 100,000 person-years in adults aged between 50 and 64 years and those aged ≥65 years, respectively. The IPD rate increased from 1.5 per 100,000 person-years in adults aged between 19 and 49 years to 3.8 and 5.9 per 100,000 person-years in adults aged between 50 and 64 years and those aged ≥65 years, respectively.

Compared with healthy adults of the same age in the JMDC database, the risk of PP in younger and older adults was highest in chronic renal disease patients (RR=23.6 [19–49 years]; RR=23.7 [≥65 years]), whereas the risk of PP in adults aged between 50 and 64 years was highest in chronic lung disease patients (R=12.8). In the MDV database, the risk of PP was highest in chronic lung disease patients across all age groups compared with healthy adults of the same age (RR=5.6 [19–49 years]; RR=6.8 [50–64 years]; RR=4.9 [≥65 years]).

Compared with healthy adults of the same age, the risk of IPD was highest in adults with cancer aged between 19 and 49 years and 50 and 64 years in the JMDC database (RR=206.6 and 26.5, respectively), whereas the risk of IPD was highest in older adults with chronic renal disease (RR=51.3). In the MDV database, the risk of IPD was highest in young adults with chronic heart disease (RR=18.4), and adults aged between 50 and 64 years and those aged ≥65 years with chronic lung disease (RR=21.4 and 4.7, respectively) compared with healthy adults of the same age.

Across all ages, PP and IPD rates were highest in adults with two or more medical conditions. PP rates in adults with two or more underlying medical conditions were nine to 17 times and three to four times the rate in healthy adults of the same age in the JMDC and MDV databases, respectively. IPD rates in adults with two or more underlying medical conditions were eight to 42 times and four to 16 times the rates in healthy adults in the JMDC and MDV databases, respectively. The PP rates in immunocompromised adults were 10 to 17 times and two to three times the rate in healthy adults of the same age in the JMDC and MDV databases, while the IPD rates were 15 to 79 times and three to 10 times the rates in healthy adults in the JMDC and MDV databases, respectively.

DISCUSSION

The Japanese Respiratory Society Guidelines for the Management of Community-Acquired Pneumonia in Adults[14] recommend pneumococcal vaccination for individuals aged between 2 and 64 years who have an underlying medical condition. However, little is known about the real-world burden of pneumococcal disease in Japanese adults with these conditions. This retrospective cohort study used two healthcare databases to evaluate the burden of pneumococcal disease in at-risk adults and adults with high-risk medical conditions to close this data gap in Japan.

Similar to previous research,[4,18,25] the principal findings of our study revealed that adults with an underlying medical condition were at increased risk of PP and IPD, compared with adults without these conditions. This was found not only among older adults aged ≥65

years but also among younger adults aged between 19 and 64 years. Our study also showed that the risk of PP and IPD increased with the number of underlying medical conditions in both younger and older adults, supporting the concept of "risk-stacking" demonstrated by previous studies.[3,17,18,29]

We also found some differences in the conditions that place individuals at increased risk of pneumococcal disease between younger and older adults. While the risk of PP and IPD was highest in older adults with chronic renal and lung diseases, the risk of PP and IPD in adults aged between 50 and 64 years was highest among patients with chronic lung disease and cancer. These results are similar to those of a previous study in which adults with chronic obstructive pulmonary disease were found to have the highest risk of IPD.[29]

In adults aged between 50 and 64 years with an underlying medical condition, PP rates in the JMDC database and IPD rates in both the JMDC and MDV databases were higher than the rates in healthy older adults aged ≥65 years, while the same trend was not observed for PP rates in the MDV database. Although pneumococcal vaccination history was not available in the two databases, the pneumococcal vaccination rate was considered low in adults aged ≥65 years during our study period, which ended in 31 December 2014. This is because there was little overlap between our study period and the National Immunization Program in Japan, which has provided a subsidy for PPV23 vaccination for adults aged ≥65 years as of 1 October 2014.[13] The influence of the subsidy for PPV23 vaccination on the PPV23 vaccination rate in adults aged ≥65 years was considered marginal during our study period. Thus, our results imply that adults aged between 50 and 64 years with an underlying medical condition may be at a greater risk of pneumococcal disease compared with healthy adults aged ≥65 years.

The 7-valent pneumococcal conjugate vaccine (PCV7) has been routinely used in children in Japan since 2010, though it has been replaced with the 13-valent PCV (PCV13) since 2013. Estimated PCV7 vaccination rates in Japan were reported to be <10% in 2010, 50%–60% in 2011, and 80%–90% in 2012.[30] Therefore, it is important to consider the potential indirect effect of the childhood PCV program on RR estimates of adult diseases,

because our study spans several years before and after the introduction of the childhood PCV program. A post-hoc analysis to explore rates and RR for PP and IPD before (2010 or earlier) and after (2011 or later) the routine use of PCVs (Supplementary Tables 2–5) demonstrated that the risk of PP and IPD in adults with an underlying medical condition remained consistently high over both time periods, suggesting that an indirect effect in adults had not yet been observed. Thus, we concluded that the childhood PCV program did not significantly impact the risk of PP and IPD in adults with an underlying medical condition during our study period.

The rates of PP and IPD were higher in the MDV than in the JMDC database in adults with and without an underlying medical condition across all age subgroups. This may not be surprising given that the two databases are drawn from different adult populations in Japan. Adults in the JMDC database represent a population of younger working adults, while those in the MDV database represent a population in need of healthcare services (i.e., hospitalised patients and outpatients). These differences in background characteristics may explain the variation in risk of PP and IPD between the two databases. Thus, the results from either database alone may not be generalizable to the general population of adults in Japan. Nonetheless, results from both databases indicate that both younger and older adults with an underlying medical condition in Japan are at increased risk of pneumococcal disease compared with healthy adults of the same age. The findings observed in Japan are consistent with similar studies conducted in the US and Germany.[3,17,18,25]

Limitations

This study had some limitations. Regarding the internal validity, using ICD-10 codes to identify medical conditions and episodes of PP and IPD may lead to misclassification. In addition, PP is often under-coded in claims data. Owing to the limited data availability in the two databases, these analyses did not consider potential confounders other than age and sex, such as pneumococcal vaccination history, residential environment, and lifestyle factors, such as smoking and drinking, which might significantly influence the risk of PP and IPD.

Regarding external validity, results from only one database cannot be extrapolated to the general population of adults in Japan, as subjects in the two databases may be representative of different adult populations.

Conclusion

Adults of all ages with an underlying medical condition, including immunocompetent and immunocompromised adults, are at greater risk of pneumococcal disease, compared with adults without any condition in Japan. This risk increases with the number of underlying medical conditions. Adults aged between 50 and 64 years with an underlying medical condition have a greater risk of pneumococcal disease than adults aged ≥65 years without any condition. Our study findings can help healthcare practitioners and policy makers identify patient groups that are vulnerable to pneumococcal disease and can benefit from pneumococcal vaccination. Adults aged ≥65 years as well as adults aged between 60 and 64 years with a specific medical condition are eligible to receive the subsidy for PPV23 under the National Immunization Program in Japan.[13] However, our results support extending the pneumococcal vaccination to younger adults with an underlying medical condition, especially those aged between 50 and 64 years.

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Disclosure

KI, AS, and SK are employees of MSD K.K., a group of Merck Sharp & Dohme Corp., which is a subsidiary of Merck & Co., Inc. (Kenilworth, NJ, USA). KN and MA received research grants and lecture fees from MSD K.K. TP and MAK are employees of Merck & Co., Inc. Employees may hold stock and/or stock options in the company. The study sponsor, Merck & Co., Inc., and MSD K.K. reviewed the study design; participated in the collection, analysis, and interpretation of the data; critically reviewed the report; and decided to submit the paper for publication.

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Author contributions

KI contributed to the conception or design of the study, and the acquisition, analysis, interpretation of the data, and drafting the manuscript. TP and MAK contributed to interpretation of the data and revision of the paper for important intellectual content. KN and MA contributed to interpretation of data and provided comments from a pulmonologist's point of view. AS contributed to analysis of the data and revision of the paper. SK contributed to the conception and design of the study, the acquisition and interpretation of data, and drafting the manuscript. All authors gave final approval of the version to be published.

Data sharing statement

Data are available on request from the corresponding author.

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Table 1. Characteristics of study subjects from the JMDC and MDV database

	JMDC					MDV				
	Cumulative number of adults	Person-years [1]		PP Events	IPD Events	Cumulative number of adults	Person-years [1]		PP Events	IPD Events
			%					%		
Overall	7,433,221	6,721,329	100	840	80	2,967,475	2,565,033	100	2,569	117
Age										
19–49 years old	5,744,222	5,211,057	78	433	28	566,908	478,300	18	117	7
50–64 years old	1,522,054	1,368,055	20	296	45	776,809	672,365	27	318	26
≥65 years old [2]	166,945	142,218	2	111	7	1,623,758	1,415,368	55	2,134	84
Sex										
Female	3,326,903	2,957,528	44	327	20	1,620,634	1,394,668	54	1,109	61
Male	4,106,318	3,763,802	56	513	60	1,346,841	1,170,364	46	1,460	56
Risk status[2]										
Healthy (no condition)	6,603,349	5,975,767	89	436	33	1,494,204	1,242,491	48	691	23
At-risk conditions	758,769	681,915	10	380	37	1,151,533	1,038,332	40	1,725	83
High-risk conditions	128,966	113,909	2	154	28	628,565	556,208	22	752	48
Medical conditions[3]										
No condition	6,603,349	5,975,767	89	436	33	1,494,204	1,242,491	48	691	23
Chronic heart disease	144,228	127,884	2	120	21	522,688	471,870	18	972	44
Chronic lung disease	313,269	281,336	4	261	19	299,695	268,656	10	1,014	37
Diabetes mellitus	283,483	253,904	4	178	31	594,890	541,680	21	761	46
Chronic liver disease	232,397	208,938	3	75	23	334,107	302,832	12	443	27
Chronic renal disease	40,585	36,286	0.5	55	6	122,872	109,707	4	217	10
Cancer	91,004	79,882	1	103	23	529,116	466,966	18	589	40
HIV/AIDS	NR	NR	NR	NR	NR	521	480	0.02	1	0
Alcoholism	2,366	2,078	0.03	1	0	2,744	2,421	0.09	4	0
Asplenia	1,732	1,538	0.02	30	16	6,799	6,031	0.2	26	1
Organ transplantation	2,525	2,214	0.03	17	16	3,895	3,535	0.1	21	2
Cerebrospinal fluid leakage	298	264	0.004	0	0	355	318	0.01	0	0
Number of conditions										
0	6,603,349	5,975,767	89	436	33	1,494,204	1,242,491	48	691	23
1	614,013	554,305	8	157	12	824,413	736,812	29	640	23
≥2	215,859	191,257	3	247	35	648,858	586,730	23	1,238	71

(1) Per 100,000 person-years, (2) Adults ≥75 years were not included in the JMDC database. Abbreviations: IPD, invasive pneumococcal disease; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; NR, not recorded; PP, pneumococcal pneumonia

(2) For risk status, some totals exceed 100% as some patients were included in more than one subcategory.
(3) For medical condition, some totals exceed 100% as some patients had more than one medical condition.

Table 2. Rates and rate ratios of pneumococcal pneumonia in the JMDC database

	All ages (≥19 years old[2])		Age subgroups					
			19–49 years old		50–64 years old		≥65 years old[2]	
	Rate[3]	RR[4] (95% CI)	Rate[3]	RR[5] (95% CI)	Rate[3]	RR[5] (95% CI)	Rate[3]	RR[5] (95% CI)
Overall	12.5		8.3		21.6		78.0	
Risk status								
Healthy (no condition)	7.3	1.0	6.3	1.0	11.5	1.0	13.2	1.0
At-risk conditions	55.7	5.3 (4.5–6.2)	33.6	5.4 (4.3–6.6)	59.1	5.0 (4.0–6.4)	180.8	8.2 (4.3–15.5)
High-risk conditions	135.2	12.9 (10.4–16.0)	104.4	17.2 (12.6–23.4)	115.0	10.2 (7.5–13.8)	325.2	16.3 (8.3–32.0)
Medical condition[1]								
No condition	7.3	1.0	6.3	1.0	11.5	1.0	13.2	1.0
Chronic heart disease	93.8	7.1 (5.7–8.8)	78.4	12.5 (8.5–18.3)	68.5	5.6 (4.0–7.8)	206.8	10.1 (5.2–19.7)
Chronic lung disease	92.8	10.8 (9.2–12.6)	51.6	8.2 (6.6–10.4)	143.1	12.8 (9.9–16.6)	356.4	18.8 (9.8–36.3)
Diabetes mellitus	70.1	5.7 (4.8–6.9)	35.9	5.7 (3.9–8.3)	65.9	5.4 (4.1–7.0)	187.9	9.0 (4.7–17.3)
Chronic liver disease	35.9	3.3 (2.6–4.3)	24.3	3.9 (2.6–5.9)	38.6	3.2 (2.2–4.7)	87.5	4.3 (2.0–9.4)
Chronic renal disease	151.6	13.4 (10.1–17.9)	148.2	23.6 (15.6–35.8)	67.8	5.6 (3.0–10.5)	517.2	23.7 (11.3–49.7)
Cancer	128.9	11.2 (9.0–14.1)	72.1	11.5 (7.4–18.0)	137.2	12.5 (9.1–17.1)	261.5	11.9 (5.8–24.1)
Number of conditions								
0	7.3	1.0	6.3	1.0	11.5	1.0	13.2	1.0
1	28.3	3.2 (2.6–3.8)	19.4	3.1 (2.3–4.1)	32.9	2.8 (2.1–3.8)	86.3	3.9 (1.9–8.0)
≥2	129.1	11.6 (9.7–13.9)	108.2	17.4 (13.4–22.6)	104.9	8.9 (6.9–11.6)	272.5	11.9 (6.2–22.8)

(1) Results of subgroups with other medical conditions, including HIV/AIDS, alcoholism, asplenia, organ transplantation, and cerebrospinal fluid leakage, are not shown.
(2) Adults ≥75 years were not included in the JMDC database.
(3) Per 100,000 person-years
(4) Age-and-sex-adjusted rate ratio
(5) Sex-adjusted rate ratio
Abbreviations: CI, confidence interval; JMDC, Japan Medical Data Center; RR, rate ratio

Table 3. Rates and rate ratios of pneumococcal pneumonia in the MDV database

	All ages (≥19 years old)		Age subgroups					
			19–49 years old		50–64 years old		≥65 years old	
	Rate[2]	RR[3] (95% CI)	Rate[2]	RR[4] (95% CI)	Rate[2]	RR[4] (95% CI)	Rate[2]	RR[4] (95% CI)
Overall	100.2		24.9		46.8		150.8	
Risk status								
Healthy (no condition)	55.6	1.0	17.8	1.0	30.2	1.0	93.0	1.0
At-risk conditions	166.1	2.3 (2.1–2.5)	50.9	2.9 (1.9–4.2)	78.4	2.5 (2.0–3.2)	216.6	2.2 (2.0–2.5)
High-risk conditions	135.2	1.8 (1.6–2.0)	48.0	2.7 (1.7–4.4)	54.0	1.7 (1.3–2.3)	177.1	1.8 (1.6–2.0)
Medical condition[1]								
No condition	55.6	1.0	17.8	1.0	30.2	1.0	93.0	1.0
Chronic heart disease	206.0	2.6 (2.3–2.9)	53.2	3.2 (1.7–6.0)	79.2	2.4 (1.8–3.2)	249.0	2.5 (2.3–2.8)
Chronic lung disease	377.4	5.2 (4.7–5.7)	97.8	5.6 (3.6–8.5)	212.1	6.8 (5.2–8.9)	479.2	4.9 (4.4–5.5)
Diabetes mellitus	140.7	1.9 (1.7–2.1)	42.7	2.6 (1.5–4.5)	60.8	1.8 (1.4–2.5)	182.1	1.8 (1.6–2.1)
Chronic liver disease	146.3	2.1 (1.9–2.4)	42.6	2.5 (1.4–4.5)	80.7	2.5 (1.9–3.4)	198.0	2.0 (1.8–2.3)
Chronic renal disease	197.8	2.6 (2.2–3.0)	85.5	5.0 (2.5–10.2)	88.3	2.7 (1.7–4.3)	248.0	2.5 (2.1–2.9)
Cancer	126.1	1.7 (1.5–1.9)	45.1	2.5 (1.5–4.3)	48.3	1.6 (1.2–2.2)	165.5	1.7 (1.5–1.9)
Number of conditions								
0	55.6	1.0	17.8	1.0	30.2	1.0	93.0	1.0
1	86.9	1.3 (1.2–1.5)	31.1	1.7 (1.1–2.7)	41.3	1.3 (1.0–1.8)	122.4	1.3 (1.1–1.4)
≥2	211.4	2.8 (2.5–3.0)	75.4	4.2 (2.6–6.7)	98.2	3.1 (2.4–4.0)	257.9	2.7 (2.4–3.0)

(1) Results of subgroups with other medical conditions, including HIV/AIDS, alcoholism, asplenia, organ transplantation, and cerebrospinal fluid leakage, are not shown.
(2) Per 100,000 person-years
(3) Age-and-sex-adjusted rate ratio
(4) Sex-adjusted rate ratio
Abbreviations: CI, confidence interval; MDV, Medical Data Vision; RR, rate ratio

Table 4. Rates and rate ratios of invasive pneumococcal diseases in the JMDC database

	All ages (≥19 years old[2])		Age subgroups					
			19–49 years old		50–64 years old		≥65 years old[2]	
	Rate[3]	RR[4] (95% CI)	Rate[3]	RR[5] (95%CI)	Rate[3]	RR[5] (95% CI)	Rate[3]	RR[5] (95% CI)
Overall	1.2		0.5		3.3		4.9	
Risk status								
Healthy (no condition)	0.6	1.0	0.3	1.0	1.6	1.0	1.2	1.0
At-risk conditions	5.4	5.3 (3.2–8.8)	1.4	4.6 (1.7–12.7)	9.3	5.7 (3.1–10.6)	11.1	4.3 (0.4–41.3)
High-risk conditions	24.6	29.7 (16.9–2.1)	20.0	79.0 (34.4–182)	28.7	18.2 (9.2–36.1)	22.7	14.9 (1.6–143)
Medical condition[1]								
No condition	0.6	1.0	0.3	1.0	1.6	1.0	1.2	1.0
Chronic heart disease	16.4	15.7 (8.8–28.0)	10.8	33.6 (11.1–102)	20.0	11.2 (5.5–22.8)	14.4	10.8 (1.1–104)
Chronic lung disease	6.8	16.4 (9.0–30.2)	0.0	0	19.7	12.9 (6.4–25.8)	26.4	5.1 (0.4–63.4)
Diabetes mellitus	12.2	12.6 (7.4–21.2)	4.8	14.7 (4.8–44.3)	16.3	10.3 (5.5–19.5)	13.7	2.8 (0.2–33.3)
Chronic liver disease	11.0	13.0 (7.5–22.7)	1.0	4.1 (0.5–31.9)	20.4	11.9 (6.2–22.9)	17.5	13.3 (1.4–128)
Chronic renal disease	16.5	25.2 (10.3–61.8)	12.4	120.7 (25.0–583)	6.2	4.2 (0.6–31.5)	77.6	51.3 (5.3–493)
Cancer	28.8	43.3 (24.7–76.2)	24.0	206.6 (80.6–530)	39.2	26.5 (13.4–525)	0.0	0
Number of conditions								
0	0.6	1.0	0.3	1.0	1.6	1.0	1.2	1.0
1	2.2	3.6 (1.8–7.1)	1.3	5.3 (1.7–16.2)	3.9	2.4 (1.0–5.5)	0.0	0
≥2	18.3	18.7 (10.9–32.1)	14.1	42.2 (18.5–96.6)	19.8	11.9 (6.2–22.8)	22.7	8.2 (0.9–79.2)

(1) Results of subgroups with other medical conditions, including HIV/AIDS, alcoholism, asplenia, organ transplantation, and cerebrospinal fluid leakage, are not shown.
(2) Adults ≥75 years were not included in the JMDC database.
(3) Per 100,000 person-years
(4) Age-and-sex-adjusted rate ratio
(5) Sex-adjusted rate ratio
Abbreviations: CI, confidence interval; JMDC, Japan Medical Data Center; RR, rate ratio

Table 5. Rates and rate ratios of invasive pneumococcal disease in the MDV database

	All ages (≥19 years old)		Age subgroups					
			19–49 years old		50–64 years old		≥65 years old	
	Rate[2]	RR[3] (95% CI)	Rate[2]	RR[4] (95% CI)	Rate[2]	RR[4] (95% CI)	Rate[1]	RR[4] (95% CI)
Overall	4.6		1.5		3.8		5.9	
Risk status								
Healthy (no condition)	1.9	1.0	0.9	1.0	0.9	1.0	3.0	1.0
At-risk conditions	8.0	3.8 (2.4–6.2)	4.0	4.0 (0.9–18.4)	7.7	9.2 (2.7–31.6)	8.7	3.0 (1.7–5.1)
High-risk conditions	8.6	4.0 (2.4–6.7)	4.2	4.7 (0.8–28.1)	8.6	9.8 (2.8–34.7)	9.2	3.1 (1.7–5.6)
Medical condition[1]								
No condition	1.9	1.0	0.9	1.0	0.9	1.0	3.0	1.0
Chronic heart disease	9.3	4.7 (2.8–7.9)	17.7	18.4 (4.0–84.2)	6.4	8.0 (2.0–32.0)	9.6	3.3 (1.8–5.8)
Chronic lung disease	13.8	7.1 (4.2–12.0)	5.9	6.5 (1.1–39.0)	18.4	21.4 (5.9–77.8)	13.8	4.7 (2.5–8.7)
Diabetes mellitus	8.5	4.4 (2.6–7.3)	10.7	11.0 (2.4–50.6)	8.5	10.4 (2.9–37.2)	8.3	2.8 (1.6–5.2)
Chronic liver disease	8.9	4.7 (2.7–8.2)	5.7	5.9 (1.0–36.1)	5.8	6.9 (1.6–28.9)	11.1	3.8 (2.0–7.2)
Chronic renal disease	9.1	4.7 (2.2–10.0)	0	0	12.6	15.4 (3.1–76.8)	9.3	3.2 (1.3–7.7)
Cancer	8.6	4.4 (2.6–7.4)	5.3	6.0 (1.0–36.2)	7.6	8.6 (2.3–31.9)	9.3	3.2 (1.8–5.9)
Number of conditions								
0	1.9	1.0	0.9	1.0	0.9	1.0	3.0	1.0
1	3.1	1.6 (0.9–2.8)	0	0	2.8	3.3 (0.8–13.4)	4.0	1.4 (0.7–2.7)
≥2	12.1	5.8 (3.6–9.5)	11.6	11.6 (2.5–54.0)	12.9	16.2 (4.7–55.7)	11.9	4.1 (2.3–7.1)

(1) Results of subgroups with other medical conditions, including HIV/AIDS, alcoholism, asplenia, organ transplantation, and cerebrospinal fluid leakage, are not shown.
(2) Per 100,000 person-years
(3) Age-and-sex-adjusted rate ratio
(4) Sex-adjusted rate ratio
Abbreviations: CI, confidence interval; MDV, Medical Data Vision; RR, rate ratio

Supplementary materials

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Abbreviations: IPD, invasive pneumococcal disease; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PP, pneumococcal pneumonia

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Supplementary Table 1. International Classification of Diseases, version 10 Codes

Condition	ICD-10 codes (2015)	Description	Disease code defined by MHLW Japan	Description	ICD-10 codes (2015)	Description	Disease code defined by MHLW Japan	Description
Chronic heart disease	I05	Rheumatic mitral valve diseases						
	I06	Rheumatic aortic valve diseases						
	I07	Rheumatic tricuspid valve diseases						
	I08	Multiple valve diseases						
	I09	Other rheumatic heart diseases						
	I11.0	Hypertensive heart disease with (congestive) heart failure						
	I13.0	Hypertensive heart and renal disease with (congestive) heart failure						
	I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure						

I20	Angina pectoris
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications following acute myocardial infarction
I24	Other acute ischaemic heart diseases
I25	Chronic ischemic heart disease
I25.1	Atherosclerotic heart disease
I25.2	Old myocardial infarction
I25.3	Aneurysm of heart
I25.4	Coronary artery aneurysm and dissection
I25.5	Ischemic cardiomyopathy
I25.6	Silent myocardial ischemia
I25.8	Other forms of chronic ischemic heart disease
I25.9	Chronic ischemic heart disease, unspecified
I27	Other pulmonary heart diseases
I34	Nonrheumatic mitral valve disorders

	I35	Nonrheumatic aortic valve disorders
	I37	Pulmonary valve disorders
	I38	Endocarditis, valve unspecified
	I42	Cardiomyopathy
	I43	Cardiomyopathy in diseases classified elsewhere
	I50	Heart failure
	I51	Complications and ill-defined descriptions of heart disease
	Q20	Congenital malformations of cardiac chambers and connections
	Q21	Congenital malformations of cardiac septa
	Q22	Congenital malformations of pulmonary and tricuspid valves
	Q23	Congenital malformations of aortic and mitral valves
	Q24	Other congenital malformations of heart
Chronic lung disease	J40	Bronchitis, not specified as acute or chronic

J41	Simple and mucopurulent chronic bronchitis
J42	Unspecified chronic bronchitis
J43	Emphysema
J44	Other chronic obstructive pulmonary disease
J45	Asthma
J46	Status asthmaticus
J47	Bronchiectasis
J60	Coalworker pneumoconiosis
J61	Pneumoconiosis due to asbestos and other mineral fibres
J62	Pneumoconiosis due to dust containing silica
J63	Pneumoconiosis due to other inorganic dusts
J64	Unspecified pneumoconiosis
J66	Airway disease due to specific organic dust
J67	Hypersensitivity pneumonitis due to organic dust
J84	Other interstitial pulmonary diseases
J96.1	Chronic respiratory failure

	J98	Other respiratory disorders
	E84	Cystic fibrosis
	I27.9	Pulmonary heart disease, unspecified
Diabetes mellitus	E10	Type 1 diabetes mellitus
	E11	Type 2 diabetes mellitus
	E12	Malnutrition-related diabetes mellitus
	E13	Other specified diabetes mellitus
	E14	Unspecified diabetes mellitus
Chronic liver disease	B16 (except B16.9)	Acute hepatitis B (except Acute hepatitis B without delta-agent and without hepatic coma)
	B17 (except B17.1)	Other acute viral hepatitis (except Acute hepatitis C)
	B18	Chronic viral hepatitis
	B19 (except B19.9)	Unspecified viral hepatitis (except Unspecified viral hepatitis without hepatic coma)
	K70	Alcoholic liver disease

	K71 (except K71.2)	Toxic liver disease (except Toxic liver disease with hepatic necrosis)
	K72 (except K72.0)	Hepatic failure, not elsewhere classified (except Acute and subacute hepatic failure)
	K73	Chronic hepatitis, not elsewhere classified
	K74	Fibrosis and cirrhosis of liver
	K75	Other inflammatory liver diseases
	K76	Other diseases of liver
	K77	Liver disorders in diseases classified elsewhere
Asplenia	D56	Thalassaemia
	D57	Sickle-cell disorders
	D60	Acquired pure red cell aplasia [erythroblastopenia]
	D61	Other aplastic anaemias
	D73.0	Hyposplenism
	D73.1	Hypersplenism
	D73.8	Other diseases of spleen
	Q89.0	Congenital malformations of spleen
	Q89.3	Situs inversus
Alcoholism	F10.2	Dependence syndrome

HIV infection	B20	Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases
	B21	Human immunodeficiency virus [HIV] disease resulting in malignant neoplasms
	B22	Human immunodeficiency virus [HIV] disease resulting in other specified diseases
	B23	Human immunodeficiency virus [HIV] disease resulting in other conditions
	B24	Unspecified human immunodeficiency virus [HIV] disease
Cancer	C00	Malignant neoplasm of lip
	C01	Malignant neoplasm of base of tongue
	C02	Malignant neoplasm of other and unspecified parts of tongue
	C03	Malignant neoplasm of gum
	C04	Malignant neoplasm of floor of mouth
	C05	Malignant neoplasm of palate

C06	Malignant neoplasm of other and unspecified parts of mouth
C07	Malignant neoplasm of parotid gland
C08	Malignant neoplasm of other and unspecified major salivary glands
C09	Malignant neoplasm of tonsil
C10	Malignant neoplasm of oropharynx
C11	Malignant neoplasm of nasopharynx
C12	Malignant neoplasm of piriform sinus
C13	Malignant neoplasm of hypopharynx
C14	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
C15	Malignant neoplasm of oesophagus
C16	Malignant neoplasm of stomach
C17	Malignant neoplasm of small intestine

C18	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21	Malignant neoplasm of anus and anal canal
C22	Malignant neoplasm of liver and intrahepatic bile ducts
C23	Malignant neoplasm of gallbladder
C24	Malignant neoplasm of other and unspecified parts of biliary tract
C25	Malignant neoplasm of pancreas
C26	Malignant neoplasm of other and ill-defined digestive organs
C30	Malignant neoplasm of nasal cavity and middle ear
C31	Malignant neoplasm of accessory sinuses
C32	Malignant neoplasm of larynx
C33	Malignant neoplasm of trachea

C34	Malignant neoplasm of bronchus and lung
C37	Malignant neoplasm of thymus
C38	Malignant neoplasm of heart, mediastinum and pleura
C39	Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs
C40	Malignant neoplasm of bone and articular cartilage of limbs
C41	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C43	Malignant melanoma of skin
C44	Other malignant neoplasms of skin
C45	Mesothelioma
C46	Kaposi sarcoma
C47	Malignant neoplasm of peripheral nerves and autonomic nervous system

C48	Malignant neoplasm of retroperitoneum and peritoneum
C49	Malignant neoplasm of other connective and soft tissue
C50	Malignant neoplasm of breast
C51	Malignant neoplasm of vulva
C52	Malignant neoplasm of vagina
C53	Malignant neoplasm of cervix uteri
C54	Malignant neoplasm of corpus uteri
C55	Malignant neoplasm of uterus, part unspecified
C56	Malignant neoplasm of ovary
C57	Malignant neoplasm of other and unspecified female genital organs
C58	Malignant neoplasm of placenta
C60	Malignant neoplasm of penis
C61	Malignant neoplasm of prostate
C62	Malignant neoplasm of testis

C63	Malignant neoplasm of other and unspecified male genital organs
C64	Malignant neoplasm of kidney, except renal pelvis
C65	Malignant neoplasm of renal pelvis
C66	Malignant neoplasm of ureter
C67	Malignant neoplasm of bladder
C68	Malignant neoplasm of other and unspecified urinary organs
C69	Malignant neoplasm of eye and adnexa
C70	Malignant neoplasm of meninges
C71	Malignant neoplasm of brain
C72	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
C73	Malignant neoplasm of thyroid gland
C74	Malignant neoplasm of adrenal gland

C75	Malignant neoplasm of other endocrine glands and related structures
C76	Malignant neoplasm of other and ill-defined sites
C77	Secondary and unspecified malignant neoplasm of lymph nodes
C78	Secondary malignant neoplasm of respiratory and digestive organs
C79	Secondary malignant neoplasm of other and unspecified sites
C80	Malignant neoplasm, without specification of site
C81	Hodgkin lymphoma
C82	Follicular lymphoma
C83	Non-follicular lymphoma
C84	Mature T/NK-cell lymphomas
C85	Other and unspecified types of non-Hodgkin lymphoma
C86	Other specified types of T/NK-cell lymphoma
C88	Malignant immunoproliferative diseases

	C90	Multiple myeloma and malignant plasma cell neoplasms
	C91	Lymphoid leukaemia
	C92	Myeloid leukaemia
	C93	Monocytic leukaemia
	C94	Other leukaemias of specified cell type
	C95	Leukaemia of unspecified cell type
	C96	Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissue
	C97	Malignant neoplasms of independent (primary) multiple sites
Chronic renal disease	I12	Hypertensive renal disease
	I13	Hypertensive heart and renal disease
	N03	Chronic nephritic syndrome
	N04	Nephrotic syndrome
	N05	Unspecified nephritic syndrome

N08	Glomerular disorders in diseases classified elsewhere		
N18	Chronic kidney disease		
N19	Unspecified kidney failure		
Q60	Renal agenesis and other reduction defects of kidney		
Q61	Cystic kidney disease		
Q62	Congenital obstructive defects of renal pelvis and congenital malformations of ureter		
Q63	Other congenital malformations of kidney		
Q64	Other congenital malformations of urinary system		
Z94.0	Kidney transplant status		
T80.9	Unspecified complication following infusion, transfusion and therapeutic injection	9999004	Renal dialysis complication
T80.9	Unspecified complication following infusion, transfusion and therapeutic injection	8842133	Dialysis disequilibrium syndrome
T80.9	Unspecified complication following infusion, transfusion and therapeutic injection	8842134	Dialysis hypotension

T80.9	Unspecified complication following infusion, transfusion and therapeutic injection	8842132	Dialysis difficulty
T82.7	Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts	8845140	Dialysis shunt infection
T82.5	Mechanical complication of other cardiac and vascular devices and implants	8845141	Dialysis shunt failure
T82.7	Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts	8847235	Dialysis shunt virtual aneurysm
T82.8	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts	8844085	Dialysis shunt stenosis
T82.8	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts	8844087	Dialysis shunt arteriovenous aneurysm
T82.8	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts	8844088	Dialysis shunt obstruction

	T82.8	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts	8844086	Dialysis shunt venous hypertension
Organ transplantation	T86	Complications of transplanted organs and tissue		
	Z94	Transplanted organ and tissue status		
Cerebrospinal fluid leakage	S06.8	Other intracranial injuries	3498002	Traumatic cerebrospinal fluid otorrhoea
	S06.8	Other intracranial injuries	3498003	Traumatic cerebrospinal fluid rhinorrhoea
	G96.0	Cerebrospinal fluid leak	3498007	Spinal leakage
	G96.0	Cerebrospinal fluid leak	8847107	Cerebrospinal fluid otorrhoea
	S06.8	Other intracranial injuries	8843154	Open traumatic cerebrospinal fluid otorrhoea
	S06.8	Other intracranial injuries	8843155	Open traumatic cerebrospinal fluid rhinorrhoea
	S06.8	Other intracranial injuries	8843261	Traumatic cerebrospinal fluid otorrhoea

	S06.8	Other intracranial injuries	8843262	Traumatic cerebrospinal fluid rhinorrhoea
	S06.8	Other intracranial injuries	8843259	Traumatic cerebrospinal fluid otorrhoea
	S06.8	Other intracranial injuries	8843260	Traumatic cerebrospinal fluid rhinorrhoea
	S06.8	Other intracranial injuries	8843531	Closed traumatic cerebrospinal fluid otorrhoea
	S06.8	Other intracranial injuries	8843532	Closed traumatic cerebrospinal rhinorrhoea
	G96.0	Cerebrospinal fluid leak	3498021	Spinal leakage
	G96.0	Cerebrospinal fluid leak	8847240	Cerebrospinal fluid leakage
	G97.0	Cerebrospinal fluid leak from spinal puncture	8836019	Cerebrospinal fluid leak from spinal puncture
Invasive pneumococcal disease	A49.1	Streptococcal infection, unspecified site	8847765	Invasive pneumococcal infection
	G00.1	Pneumococcal meningitis	3201001	Pneumococcal meningitis

A40.3	Sepsis due to Streptococcus pneumoniae	8838800	Pneumococcal sepsis					
A49.9	Bacterial infection, unspecified	7907001	Bacteraemia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
A41.9	Sepsis, unspecified	0389004	Sepsis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
G04.2	Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified	8831417	Purulent cerebral meningitis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
G03.9	Meningitis, unspecified	3229007	Meningitis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
G04.9	Encephalitis, myelitis and encephalomyelitis, unspecified	3239028	Myelomeningitis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
I33.0	Acute and subacute infective endocarditis	8838820	Septic endocarditis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection

I30.1	Infective pericarditis	8838821	Septic pericarditis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
J20.9	Acute bronchitis, unspecified	8838818	Septic bronchitis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
J18.9	Pneumonia, unspecified	8838823	Septic pneumonia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
A49.9	Bacterial infection, unspecified	0389014	Transient bacteraemia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
A49.9	Bacterial infection, unspecified	0389015	Intermittent bacteraemia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
A49.9	Bacterial infection, unspecified	0389016	Persistent bacteraemia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
A49.9	Bacterial infection, unspecified	7907001	Bacteraemia	and	A49.1	Streptococcal infection,	8847809	Pneumococcal infection

	A41.9	Sepsis, unspecified organism			and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	M86.9	Osteomyelitis, unspecified	8838819	Septic osteomyelitis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	A41.8	Other specified sepsis	8847009	Gram-positive bacterial sepsis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
Pneumococcal pneumonia	J13	Pneumonia due to Streptococcus pneumoniae	8838802	Pneumococcal pneumonia					
	J20.2	Acute bronchitis due to streptococcus	8838798	Pneumococcal bronchitis					
	J15.9	Bacterial pneumonia, unspecified	4829003	Bacterial pneumonia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	J18	Pneumonia, organism unspecified	8832171	Bronchopneumonia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection

	J18	Pneumonia, organism unspecified	4860030	Pneumonia	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	J86	Pyothorax			and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	J90	Pleural effusion, not elsewhere classified			and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	J91	Pleural effusion in other conditions classified elsewhere			and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
Exclusion criteria (below)									
	A49.9	Bacterial infection, unspecified	7907001	Bacteraemia					
	A49.9	Bacterial infection, unspecified	0389014	Transient bacteraemia					
	A49.9	Bacterial infection, unspecified	0389015	Intermittent bacteraemia					
	A49.9	Bacterial infection, unspecified	0389016	Persistent bacteraemia					

A41.9	Sepsis, unspecified organism		
A41.8	Other specified sepsis	8847009	Gram-positive bacterial sepsis

Supplementary Table 2. Rates and rate ratios of pneumococcal pneumonia in the JMDC database

	Pre-PCV era		Post-PCV era			
	2006–2010[2]		2011–2012[2]		2013–2014[2]	
	Rate[3]	RR[4] (95% CI)	Rate[3]	RR[4] (95% CI)	Rate[3]	RR[4] (95% CI)
Overall	8.1		14.2		15.6	
Risk status						
Healthy (no condition)	5.5	1.0	8.7	1.0	7.7	1.0
At-risk conditions	33.9	4.8 (3.5–6.7)	58.7	5.0 (3.8–6.4)	68.3	6.4 (5.0–8.1)
High-risk conditions	92.9	13.3 (8.4–20.9)	161.3	13.9 (10.2–19.1)	139.6	13.5 (9.6–19.0)
Medical condition[1]						
No condition	5.5	1.0	8.7	1.0	7.7	1.0
Chronic heart disease	30.3	3.0 (1.5–5.9)	120.7	10.1 (7.1–14.5)	112.0	10.1 (7.1–14.6)
Chronic lung disease	53.8	8.7 (6.1–12.4)	92.8	9.3 (7.2–12.0)	122.2	13.1 (10.2–16.8)
Diabetes mellitus	34.9	3.9 (2.4–6.4)	71.5	5.3 (3.8–7.3)	91.0	8.2 (6.0–11.1)
Chronic liver disease	39.9	5.3 (3.3–8.5)	27.0	2.5 (1.6–4.0)	41.5	4.1 (2.7–6.1)
Chronic renal disease	20.6	2.7 (0.7–11.0)	234.9	19.2 (12.6–29.1)	166.8	17.9 (11.2–28.5)
Cancer	95.2	13.6 (8.0–23.1)	134.6	12.1 (8.2–17.7)	145.5	12.9 (8.8–18.8)
Number of conditions						
0	5.5	1.0	8.7	1.0	7.7	1.0
1	18.5	3.0 (1.9–4.5)	27.7	2.7 (2.0–3.7)	36.1	3.9 (2.9–5.2)
≥2	85.5	11.6 (7.8–17.2)	140.8	11.4 (8.6–15.1)	146.8	13.0 (9.8–17.3)

(1) Results of subgroups with other medical conditions, including HIV/AIDS, alcoholism, asplenia, organ transplantation, and cerebrospinal fluid leakage, are not shown.
(2) Adults ≥75 years were not included in the JMDC database.
(3) Per 100,000 person-years
(4) Age-and-sex-adjusted rate ratio

Abbreviations: CI, confidence interval; JMDC, Japan Medical Data Center; PCV, pneumococcal conjugate vaccine; RR, rate ratio

Supplementary Table 3. Rates and rate ratios of pneumococcal pneumonia in the MDV database

	Pre-PCV era		Post-PCV era			
	2009–2010		2011–2012		2006–2010	
	Rate[2]	RR[3] (95% CI)	Rate[2]	RR[3] (95% CI)	Rate[2]	RR[3] (95% CI)
Overall	92.3		90.9		94.5	
Risk status						
Healthy (no condition)	60.5	1.0	56.1	1.0	66.1	1.0
At-risk conditions	169.9	2.0 (1.6–2.4)	180.6	2.5 (2.3–2.7)	159.0	2.1 (1.9–2.3)
High-risk conditions	110.1	1.3 (1.0–1.7)	133.9	1.8 (1.5–2.0)	137.1	1.7 (1.6–1.9)
Medical condition[1]						
No condition	60.5	1.0	56.1	1.0	66.1	1.0
Chronic heart disease	213.4	2.3 (1.8–2.9)	227.4	2.8 (2.5–3.1)	195.9	2.3 (2.1–2.6)
Chronic lung disease	403.2	4.7 (3.8–6.0)	435.3	5.9 (5.3–6.6)	349.6	4.5 (4.1–5.0)
Diabetes mellitus	143.8	1.6 (1.2–2.1)	140.0	1.9 (1.6–2.1)	141.7	1.8 (1.6–2.0)
Chronic liver disease	115.7	1.5 (1.1–2.1)	145.3	2.1 (1.8–2.5)	134.0	1.8 (1.6–2.1)
Chronic renal disease	172.1	2.0 (1.2–3.1)	184.7	2.4 (2.0–3.0)	198.7	2.5 (2.2–2.9)
Cancer	104.1	1.2 (0.9–1.6)	127.1	1.7 (1.4–1.9)	128.8	1.6 (1.4–1.8)
Number of conditions						
0	60.5	1.0	56.1	1.0	66.1	1.0
1	97.7	1.3 (1.0–1.6)	100.6	1.5 (1.3–1.7)	84.0	1.2 (1.1–1.3)
≥2	205.5	2.2 (1.8–2.8)	227.3	2.9 (2.6–3.2)	206.9	2.5 (2.3–2.8)

(1) Results of subgroups with other medical conditions, including HIV/AIDS, alcoholism, asplenia, organ transplantation, and cerebrospinal fluid leakage, are not shown.
(2) Per 100,000 person-years
(3) Age-and-sex-adjusted rate ratio
Abbreviations: CI, confidence interval; MDV, Medical Data Vision; PCV, pneumococcal conjugate vaccine; RR, rate ratio

Supplementary Table 4. Rates and rate ratios of invasive pneumococcal diseases in the JMDC database

	Pre-PCV era		Post-PCV era			
	2006–2010[2]		2011–2012[2]		2006–2010[2]	
	Rate[3]	RR[4] (95% CI)	Rate[3]	RR[4] (95% CI)	Rate[3]	RR[4] (95% CI)
Overall	0.4		1.7		1.4	
Risk status						
Healthy (no condition)	0.3	1.0	0.7	1.0	0.7	1.0
At-risk conditions	2.2	3.5 (1.0–12.5)	8.7	6.5 (3.2–13.2)	4.6	4.9 (2.1–11.3)
High-risk conditions	0.0	--	42.2	44.8 (20.0–100.1)	24.8	32.1 (13.0–79.2)
Medical condition[1]						
No condition	0.3	1.0	0.7	1.0	0.7	1.0
Chronic heart disease	0.0	--	24.6	14.5 (6.0–35.2)	20.0	24.2 (9.3–63.2)
Chronic lung disease	1.3	3.0 (0.4–24.8)	10.1	10.8 (4.7–24.8)	7.7	8.4 (3.4–20.8)
Diabetes mellitus	4.8	5.5 (1.4–22.3)	19.0	11.3 (5.2–24.6)	10.9	11.7 (4.6–29.5)
Chronic liver disease	3.6	5.4 (1.1–26.6)	20.3	14.7 (6.8–31.9)	7.5	6.2 (2.2–17.4)
Chronic renal disease	0.0	--	15.7	9.2 (1.9–44.0)	29.0	31.0 (9.2–104.6)
Cancer	0.0	--	53.1	67.9 (29.3–157.6)	25.3	34.5 (12.8–92.7)
Number of conditions						
0	0.3	1.0	0.7	1.0	0.7	1.0
1	1.3	2.3 (0.5–11.4)	2.6	3.2 (1.5–6.9)	2.4	1.2 (0.5–2.6)
≥2	4.2	5.0 (1.0–25.0)	31.1	4.4 (1.4–13.6)	15.9	1.0 (0.2–4.6)

(1) Results of subgroups with other medical conditions, including HIV/AIDS, alcoholism, asplenia, organ transplantation, and cerebrospinal fluid leakage, are not shown.
(2) Adults ≥75 years were not included in the JMDC database.
(3) Per 100,000 person-years
(4) Age-and-sex-adjusted rate ratio

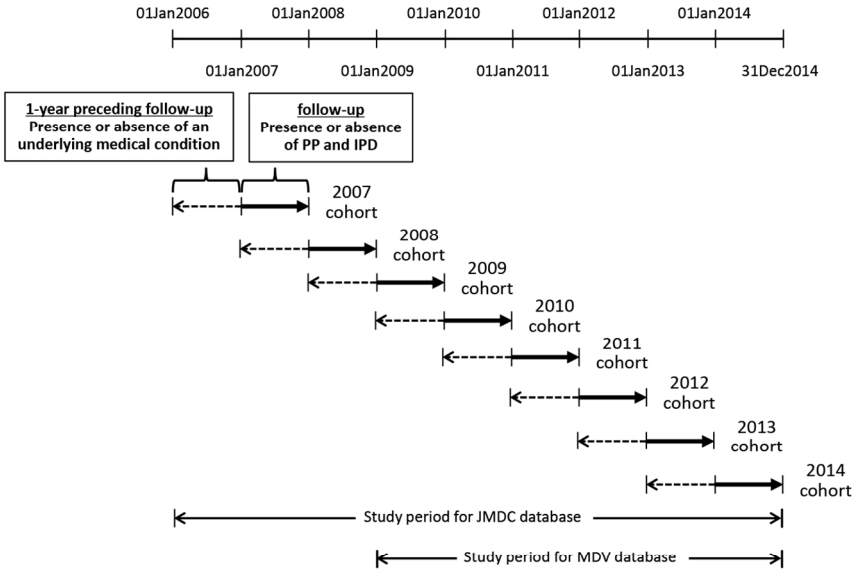
Abbreviations: CI, confidence interval; JMDC, Japan Medical Data Center; PCV, pneumococcal conjugate vaccine; RR, rate ratio

Supplementary Table 5. Rates and rate ratios of invasive pneumococcal disease in the MDV database

	Pre-PCV era		Post-PCV era			
	2009–2010		2011–2012		2009–2010	
	Rate[2]	RR[3] (95% CI)	Rate[2]	RR[3] (95% CI)	Rate[2]	RR[3] (95% CI)
Overall	3.8		3.3		4.8	
Risk status						
Healthy (no condition)	3.4	1.0	1.8	1.0	2.7	1.0
At-risk conditions	4.2	0.8 (0.3–2.4)	6.7	3.0 (1.8–5.2)	8.7	3.3 (2.2–4.9)
High-risk conditions	5.4	1.1 (0.3–3.6)	8.0	3.6 (2.0–6.7)	11.5	4.3 (2.8–6.5)
Medical condition[1]						
No condition	3.4	1.0	1.8	1.0	2.7	1.0
Chronic heart disease	1.5	0.3 (0.03–2.2)	7.9	3.1 (1.6–5.8)	9.7	3.3 (2.1–5.3)
Chronic lung disease	8.4	1.6 (0.4–6.1)	10.0	4.4 (2.2–8.7)	16.6	6.2 (3.9–9.9)
Diabetes mellitus	4.3	0.8 (0.2–3.0)	8.2	3.5 (1.9–6.4)	8.9	6.2 (2.0–5.0)
Chronic liver disease	7.5	1.5 (0.4–5.5)	8.1	3.9 (2.0–7.7)	9.3	3.4 (2.0–5.7)
Chronic renal disease	0.0	--	8.6	4.0 (1.5–10.8)	14.1	4.7 (2.6–8.6)
Cancer	4.7	0.9 (0.2–3.3)	8.7	4.0 (2.1–7.4)	11.0	4.0 (2.6–6.2)
Number of conditions						
0	3.4	1.0	1.8	1.0	2.7	1.0
1	3.8	0.8 (0.3–2.6)	2.2	1.1 (0.5–2.4)	3.5	1.4 (0.8–2.3)
≥2	5.2	1.0 (0.3–3.3)	11.3	5.0 (2.8–8.8)	13.8	5.3 (3.5–7.9)

(1) Results of subgroups with other medical conditions, including HIV/AIDS, alcoholism, asplenia, organ transplantation, and cerebrospinal fluid leakage, are not shown.
(2) Per 100,000 person-years
(3) Age-and-sex-adjusted rate ratio
Abbreviations: CI, confidence interval; MDV, Medical Data Vision; PCV, pneumococcal conjugate vaccine; RR, rate ratio

Supplementary Figure 1.



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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Reported on page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1 Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2 Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P4-P5
Objectives	3	State specific objectives, including any prespecified hypotheses	P5, L17-22
Methods			
Study design	4	Present key elements of study design early in the paper	P2-P5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P5-P8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	P6 Study design and population
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	P6 Study design and population
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P6-P7 Study variables
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P5 Data source
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	P6 Study design and population
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6-P7 Study variables
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P7-P8 Statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	P7 Study variables
		(*d*) If applicable, explain how loss to follow-up was addressed	P7 Study variables
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P8 Characteristics of the study population
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	P8 Characteristics

		confounders	of the study population
		(b) Indicate number of participants with missing data for each variable of interest	P8 Characteristics of the study population
		(c) Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures over time	P8-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P8-10
		(*b*) Report category boundaries when continuous variables were categorized	P8-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P8-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	P10 Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P11-12 Limitation
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	P12 conclusion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P13 Funding

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.