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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. 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. 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. 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. Subjects in the MDV database can be lost to follow-up. Both databases have been used in multiple studies published in peer-reviewed journals.

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 Japan²⁷ 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 Adults¹⁴ 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. 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. 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, and interpretation of the data, ...
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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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Supplementary Figure 1. Study design

Abbreviations: IPD, invasive pneumococcal disease; JMDC, Japan Medical Data Center;

MDV, Medical Data Vision; PP, pneumococcal pneumonia



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

	All ages			re aubaroupe 7			
/~		L		je subgroups 2	> 05 (2)		
						≥65 years old ⁽²⁾	
Rate ⁽³⁾	RR ⁽⁴⁾ (95% CI)	Rate (3)	RR ⁽⁵⁾ (95% CI)	Rate ⁽³⁾	RR ⁽⁵⁾ (95% CI <u>)</u> 2	Rate ⁽³⁾	RR ⁽⁵⁾ (95% CI)
12.5		8.3		21.6	Οον	78.0	
					vnlo		
7.3	1.0	6.3	1.0	11.5	1.0 a	13.2	1.0
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)
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)
					ht		
7.3	1.0	6.3	1.0	11.5	1.0	13.2	1.0
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)
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)
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)
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)
151.6	13.4 (10.1–17.9)	148.2	23.6 (15.6–35.8)	67.8	5.6 (3.0–10.5) <mark>8</mark>	517.2	23.7 (11.3–49.7)
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)
					on ,		
7.3	1.0	6.3	1.0	11.5	1.0 ਊ	13.2	1.0
28.3	3.2 (2.6–3.8)	19.4	3.1 (2.3–4.1)	32.9	2.8 (2.1–3.8) <u>a</u>	86.3	3.9 (1.9–8.0)
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)
	Rate ⁽³⁾ 12.5 7.3 55.7 135.2 7.3 93.8 92.8 70.1 35.9 151.6 128.9 7.3 28.3 129.1	7.3 1.0 55.7 5.3 (4.5–6.2) 135.2 12.9 (10.4–16.0) 7.3 1.0 93.8 7.1 (5.7–8.8) 92.8 10.8 (9.2–12.6) 70.1 5.7 (4.8–6.9) 35.9 3.3 (2.6–4.3) 151.6 13.4 (10.1–17.9) 128.9 11.2 (9.0–14.1) 7.3 1.0 28.3 3.2 (2.6–3.8)	(≥19 years old ⁽²⁾) Rate ⁽³⁾ RR(⁽⁴⁾ (95% CI) Rate ⁽³⁾ Rate ⁽³⁾ RR(⁽⁴⁾ (95% CI) Rate ⁽³⁾ Rate ⁽³⁾ Rate ⁽³⁾ RR(⁽⁴⁾ (95% CI) Rate ⁽³⁾ Rate ⁽⁴⁾ Rate ⁽³⁾ Rate ⁽⁴⁾ Rate ⁽⁴⁾ Rate ⁽⁴⁾ Rate ⁽³⁾ Rate ⁽⁴⁾ R	(≥19 years old²²) 19–49 years old Rate³³ RR⁴³ (95% CI) Rate ³³ RR⁵⁵ (95% CI) 12.5 8.3 7.3 1.0 6.3 1.0 55.7 5.3 (4.5–6.2) 33.6 5.4 (4.3–6.6) 135.2 12.9 (10.4–16.0) 104.4 17.2 (12.6–23.4) 7.3 1.0 6.3 1.0 93.8 7.1 (5.7–8.8) 78.4 12.5 (8.5–18.3) 92.8 10.8 (9.2–12.6) 51.6 8.2 (6.6–10.4) 70.1 5.7 (4.8–6.9) 35.9 5.7 (3.9–8.3) 35.9 3.3 (2.6–4.3) 24.3 3.9 (2.6–5.9) 151.6 13.4 (10.1–17.9) 148.2 23.6 (15.6–35.8) 128.9 11.2 (9.0–14.1) 72.1 11.5 (7.4–18.0) 7.3 1.0 6.3 1.0 28.3 3.2 (2.6–3.8) 19.4 3.1 (2.3–4.1) 129.1 11.6 (9.7–13.9) 108.2 17.4 (13.4–22.6)	(\geq 19 years old ⁽²⁾) 19–49 years old 50 Rate ⁽³⁾ RR ⁽⁴⁾ (95% CI) Rate ⁽³⁾ RR ⁽⁵⁾ (95% CI) Rate ⁽³⁾ 12.5 8.3 21.6 7.3 1.0 6.3 1.0 11.5 55.7 5.3 (4.5–6.2) 33.6 5.4 (4.3–6.6) 59.1 135.2 12.9 (10.4–16.0) 104.4 17.2 (12.6–23.4) 115.0 7.3 1.0 6.3 1.0 11.5 93.8 7.1 (5.7–8.8) 78.4 12.5 (8.5–18.3) 68.5 92.8 10.8 (9.2–12.6) 51.6 8.2 (6.6–10.4) 143.1 70.1 5.7 (4.8–6.9) 35.9 5.7 (3.9–8.3) 65.9 35.9 3.3 (2.6–4.3) 24.3 3.9 (2.6–5.9) 38.6 151.6 13.4 (10.1–17.9) 148.2 23.6 (15.6–35.8) 67.8 128.9 11.2 (9.0–14.1) 72.1 11.5 (7.4–18.0) 137.2 7.3 1.0 6.3 1.0 11.5 28.3 3.2 (2.6–3.8) 19.4 3.1	(≥19 years old²) 19–49 years old 50–64 years old 2 Rate³³ RR⁴³ (95% Cl) Rate³³ RR⁵⁵ (95% Cl) Rate³³ RR⁶⁵ (95% Cl) 12.5 8.3 21.6 8.3 21.6 8.3 21.6 8.3 21.6 8.3 21.6 8.3 21.6 8.3 21.6 8.3 21.6 8.3 21.6 8.3 21.6 8.3 21.6 8.3 21.6 8.3 21.6 8.3 21.6 8.3 21.6 8.3 21.6 8.3 21.6 8.3 21.6 8.3 8.3 8.4 8.3 8.4 8.3 8.4 8.3 8.4 8.3 8.3 8.4 8.3 8.3 8.4 8.3	(≥19 years old(²)) 19–49 years old 50–64 years old ≥ Rate(³) RR(³) (95% CI) Rate(³) RR(⁵) (95% CI) Rate(³) Rate(³)

| ≥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

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

		All ages			Age	e subgroups କ୍ର		
		years old)	19-	-49 years old	-64 years old		≥65 years old	
	Rate ⁽²⁾	RR ⁽³⁾ (95% CI)	Rate ⁽²⁾	RR ⁽⁴⁾ (95% CI)	Rate ⁽²⁾	RR ⁽⁴⁾ (95% CI) S	Rate ⁽²⁾	RR ⁽⁴⁾ (95% CI)
Overall	100.2		24.9		46.8	8. [150.8	
Risk status						Ow		
Healthy (no condition)	55.6	1.0	17.8	1.0	30.2	1.0 nlo	93.0	1.0
Immunocompetent	166.1	2.3 (2.1–2.5)	50.9	2.9 (1.9-4.2)	78.4	$2.5 (2.0-3.2) \frac{a}{c}$	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⁾						rom		
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) 8	165.5	1.7 (1.5–1.9)
Number of conditions						, m		
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) ថ្មី	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) ,9	257.9	2.7 (2.4–3.0)

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

		All ages	Age subgroups ≅							
	(≥	19 years old ⁽²⁾)	19–49 years old			50–64 years old 을		≥65 years old ⁽²⁾		
	Rate ⁽³⁾	RR ⁽⁴⁾ (95% CI)	Rate ⁽³⁾ RR ⁽⁵⁾ (95%CI)		Rate ⁽³⁾ RR ⁽⁵⁾ (95% CR)		Rate ⁽³⁾	RR ⁽⁵⁾ (95% CI)		
Overall	1.2		0.5		3.3	8. [4.9			
Risk status						Оом				
Healthy (no condition)	0.6	1.0	0.3	1.0	1.6	1.0 nlo	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 (3.1–10.5)	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 🖺)	22.7	14.9 (1.6–143)		
Medical condition ⁽¹⁾						rom				
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🕱)	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🕏)	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 (6.2–22.39)	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						m/ o				
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 (6.2–22.3)	22.7	8.2 (0.9–79.2)		

| ≥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

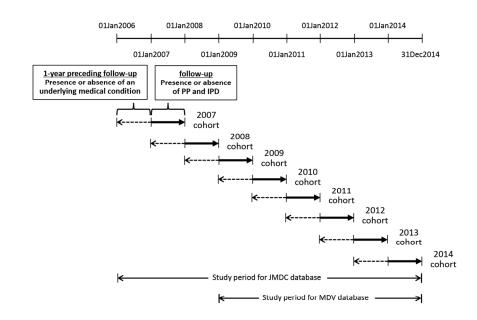
Table 4. Rates and rate ratios of invasive pneumococcal disease in the MDV database

		All ages	Age subgroups ু						
	(≥1	9 years old)	19	19-49 years old		–64 years old ⊃	≥65 years old		
	Rate ⁽²⁾	RR ⁽³⁾ (95% CI)	Rate ⁽²⁾	RR ⁽⁴⁾ (95% CI)	Rate ⁽²⁾	RR ⁽⁴⁾ (95% 🖼)	Rate ⁽¹⁾	RR ⁽⁴⁾ (95% CI)	
Overall	4.6		1.5	-	3.8	8. [5.9	-	
Risk status						Оом			
Healthy (no condition)	1.9	1.0	0.9	1.0	0.9	1.0 nl	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 (2.7–31.3)	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. Ž)	9.2	3.1 (1.7–5.6)	
Medical condition ⁽¹⁾						om			
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🕏)	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😲)	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. <mark>9</mark>)	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 (3.1–763)	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						D / 0			
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, \$\vec{\varphi})	11.9	4.1 (2.3–7.1)	

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Supplementary Table 1. Characte	eristics of study s	subjects from	the JMDC	and MD	V databa	se	on 2			
		JMD)C		1		 <u>≅</u> MD	11/		
	Cumulative	Person-ye		PP	IPD	Cumulative	Person-ye		PP	IPD
	number of	r erson-ye	%	Events	Events	number of	N	%	Events	Events
	adults		70	LVCIIIS	LVCIIIS	adults	018	70	LVCIIIS	LVEIIIS
Overall	7,433,221	6,721,329	100%	840	80	2,967,475	2,565,033	100%	2,569	117
Age							W			
19–49 years old	5,744,222	5,211,057	78%	433	28	566,908	47 ₿ ,300	18%	117	7
50-64 years old	1,522,054	1,368,055	20%	296	45	776,809	67 2 ,365	26%	318	26
≥65 years old ⁽²⁾	166,945	142,218	2%	111	7	1,623,758	1,41 5 ,368	55%	2,134	84
Sex							fro			
Female	3,326,903	2,957,528	44%	327	20	1,620,634	1,39 4 ,668	54%	1,109	61
Male	4,106,318	3,763,802	56%	513	60	1,346,841	1,173,364	46%	1,460	56
Risk status							<u>``</u>			
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	1,03 <mark>8</mark> ,332	40%	1,725	83
Immunocompromised	128,966	113,909	2%	154	28	628,565	55 <mark>8</mark> ,208	22%	752	48
Medical conditions					,		bm bm		,	
No condition	6,603,349	5,975,767	89%	436	33	1,494,204	1,24 <mark>2</mark> ,491	48%	691	23
Chronic heart disease	144,228	127,884	2%	120	21	522,688	47 <mark>3</mark> ,870	18%	972	44
Chronic lung disease	313,269	281,336	4%	261	19	299,695	26 <u>8</u> ,656	10%	1,014	37
Diabetes mellitus	283,483	253,904	4%	178	31	594,890	54₫,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	10\overline{3},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)2480)24	0.02%	1	0
Alcoholism	2,366	2,078	0.03%	1	0	2,744	₹,421	0.09%	4	0
Asplenia	1,732	1,538	0.02%	30	16	6,799	<u>6,031</u>	0.2%	26	1
Organ transplantation	2,525	2,214	0.03%	17	16	3,895	8 ,535	0.1%	21	2
Cerebrospinal fluid leakage	298	264	0.004%	0	0	355	^{5†} 318	0.01%	0	0
Number of conditions	0.000.040	E 07E 707	000/	400	00	4 404 004	1 0475 404	400/	004	00
0	6,603,349	5,975,767	89%	436	33	1,494,204	1,240,491	48%	691	23
1	614,013	554,305	8%	157	12	824,413	73 6 ,812	29%	640	23
≥2 (1) Per 100 000 person-years (2)	215,859	191,257	3%	247	35	648,858	58 5 ,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.



127x95mm (300 x 300 DPI)

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ICD-10

codes (2015) Description

Disease

defined by

code

MHLW

Japan

Description

Condition	ICD-10 codes	Description	Disease code defined by MHLW	Description
	(2015)		Japan	2 March 2018. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright
Chronic heart disease	105	Rheumatic mitral valve diseases		2018. [
	106	Rheumatic aortic valve diseases		Ook
	107	Rheumatic tricuspid valve diseases		j
	108	Multiple valve diseases		рас
	109	Other rheumatic heart diseases		ed
	I11.0	Hypertensive heart disease with (congestive) heart failure		from
	I13.0	Hypertensive heart and renal disease with (congestive) heart failure		http://b
	I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure		mjoper
	120	Angina pectoris		1.bi
	121	Acute myocardial infarction		3.
	122	Subsequent myocardial infarction		S S
	123	Certain current complications following acute myocardial infarction		n/ on /
	124	Other acute ischaemic heart diseases		δpr
	125	Chronic ischemic heart disease		<u>=</u> :
	I25.1	Atherosclerotic heart disease		,- <u>N</u>
	125.2	Old myocardial infarction		022
	125.3	Aneurysm of heart		Ġ
	125.4	Coronary artery aneurysm and dissection		9
	125.5	Ischemic cardiomyopathy		ues
	125.6	Silent myocardial ischemia		
	125.8	Other forms of chronic ischemic heart disease		Protec
	125.9	Chronic ischemic heart disease, unspecified		tec
	127	Other pulmonary heart diseases		þ
	134	Nonrheumatic mitral valve disorders		ς.
	135	Nonrheumatic aortic valve disorders		ору
	137	Pulmonary valve disorders		'nig
	138	Endocarditis, valve unspecified		₽.

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				_{9n-20}
				317-
	142	Cardiomyopathy		7-018553
		Cardiomyopathy in diseases classified		
	I43	elsewhere		9
	150	Heart failure		N Z
	I51	Complications and ill-defined descriptions of heart disease		March 2
	Q20	Congenital malformations of cardiac chambers and connections		2018
	Q21	Congenital malformations of cardiac septa		•
	Q22	Congenital malformations of pulmonary and		Down
		tricuspid valves		
	Q23	Congenital malformations of aortic and mitral valves		de ed
	Q24	Other congenital malformations of heart		fror
Chronic lung disease	J40	Bronchitis, not specified as acute or chronic		http
	J41	Simple and mucopurulent chronic bronchitis		://
	J42	Unspecified chronic bronchitis		D io
	J43	Emphysema		စို
	J44	Other chronic obstructive pulmonary disease		<u>, p</u>
	J45	Asthma		른
	J46	Status asthmaticus		COT TO THE PROPERTY OF THE PRO
	J47	Bronchiectasis		
	J60	Coalworker pneumoconiosis		
	J61	Pneumoconiosis due to asbestos and other mineral fibres		.bmj.com/ on April 9, 2024
	J62	Pneumoconiosis due to dust containing silica		, 20
	J63	Pneumoconiosis due to other inorganic dusts		022
	J64 J66	Unspecified pneumoconiosis		
		Airway disease due to specific organic dust Hypersensitivity pneumonitis due to organic	4	ر ال
	J67	dust		by guest.
	J84	Other interstitial pulmonary diseases		P
	J96.1	Chronic respiratory failure		O te
	J98	Other respiratory disorders		otected
	E84	Cystic fibrosis		by
	127.9	Pulmonary heart disease, unspecified		
Diabetes mellitus	E10	Type 1 diabetes mellitus		;opyright
	E11	Type 2 diabetes mellitus		√ri 9
	E12	Malnutrition-related diabetes mellitus		h.

Page 27 of 37				BMJ Open	bmjopen
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1					17-
2					
3 4		E13 E14	Other specified diabetes mellitus Unspecified diabetes mellitus		8553
5		B16	Acute hepatitis B (except Acute hepatitis B		<u> </u>
6	Chronic liver disease	(except	without delta-agent and without hepatic		N ≤
7	G.:000.00	B16.9)	coma)		March
8		B17	Other acute viral hepatitis (except Acute		ה א
9		(except B17.1)	hepatitis C)		2018
10 11		B17.1) B18	Chronic viral hepatitis		•
12		B19	Unspecified viral hepatitis (except		Dow
13		(except	Unspecified viral hepatitis without hepatic		
14		B19.9)	coma)		ade
15		K70 [′]	Alcoholic liver disease		<u>ਲ</u> ੇ ਜ
16		K71	Toxic liver disease (exceptToxic liver disease		ron .
17		(except	with hepatic necrosis)		₹ 2
18		K71.2)	with hepatic hecrosis)		.tb :
19		K72	Hepatic failure, not elsewhere classified		//br
20		(except	(except Acute and subacute hepatic failure)		<u>a</u> .
21		K72.0)			pen
22		K73 K74	Chronic hepatitis, not elsewhere classified Fibrosis and cirrhosis of liver		- b
23		K74 K75	Other inflammatory liver diseases		<u>⊐</u> . c
24		K75 K76	Other diseases of liver		Ö T
25			Liver disorders in diseases classified		9
26		K77	elsewhere		→
27	Asplenia	D56	Thalassaemia		D
28		D57	Sickle-cell disorders		bmj.com/ on April 9, 2024
29		D60	Acquired pure red cell aplasia		202
30			[erythroblastopenia]		
31		D61	Other aplastic anaemias		by guest.
32		D73.0	Hyposplenism		0.00
33		D73.1	Hypersplenism		
34		D73.8	Other diseases of spleen		Pro
35		Q89.0	Congenital malformations of spleen		otecte
36	Alcoholism	Q89.3 F10.2	Situs inversus		<u>Θ΄</u> Q.
37	Alcoholism	F IU.∠	Dependence syndrome Human immunodeficiency virus [HIV]		\$
38	HIV infection	B20	disease resulting in infectious and parasitic		copyright.
39	THE IIIICOUOII	520	diseases		угі
40		B21	Human immunodeficiency virus [HIV]		g ht
41		 .	The second secon		;·
42					

			BMJ Open	Page 1997 - 2017 - 018553 on 2	age 28 of 3
			•	.2017-(
		disease resulting in malignant neoplasms	;	01 8553	
	B22	Human immunodeficiency virus [HIV] disease resulting in other specified diseases	,	on	
	B23	Human immunodeficiency virus [HIV]			
	D20	disease resulting in other conditions	7	flarc	
	B24	Unspecified human immunodeficiency virus [HIV] disease	:	March 20	
Cancer	C00	Malignant neoplasm of lip		18.	
	C01	Malignant neoplasm of base of tongue		Do	
	C02	Malignant neoplasm of other and unspecified	•	<u>n_</u>	
	C03	parts of tongue Malignant neoplasm of gum	,	o ad	
	C04	Malignant neoplasm of floor of mouth	•	e d	
	C05	Malignant neoplasm of palate	.	fror	
	C06	Malignant neoplasm of other and unspecified	.	<u>고</u>	
		parts of mouth			
	C07	Malignant peoplesm of other and unspecified	N _L	Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest.	
	C08	Malignant neoplasm of other and unspecified major salivary glands	- L	a) op	
	C09	Malignant neoplasm of tonsil		en.	
	C10	Malignant neoplasm of torish		<u> </u>	
	C11	Malignant neoplasm of nasopharynx		j.co	
	C12	Malignant neoplasm of piriform sinus	(0)		
	C13	Malignant neoplasm of hypopharynx			
	C14	Malignant neoplasm of other and ill-defined	·	Apri	
	C15	sites in the lip, oral cavity and pharynx Malignant neoplasm of oesophagus	•	9,9	
	C16	Malignant neoplasm of desophagus Malignant neoplasm of stomach		20	
	C17	Malignant neoplasm of small intestine	,	24!	
	C18	Malignant neoplasm of colon	,	δy ξ	
	C19	Malignant neoplasm of rectosigmoid junction	7	gue.	
	C20	Malignant neoplasm of rectum	,	St. F	
	C21	Malignant neoplasm of anus and anal canal Malignant neoplasm of liver and intrahepatic		9 ₇₀₁	
	C22	bile ducts	•	Protected by copyright.	
	C23	Malignant neoplasm of gallbladder	,	e <u>a </u>	
	C24	Malignant neoplasm of other and unspecified	,,	by c	
		parts of biliary tract	.7	ор ,	
	C25	Malignant neoplasm of pancreas		Уri g	
	C26	Malignant neoplasm of other and ill-defined	-	,	

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45 46 47 BMJ Open

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C90

lymphoma

neoplasms

Other specified types of T/NK-cell lymphoma

Multiple myeloma and malignant plasma cell

Malignant immunoproliferative diseases

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1 2					omjopen-2017-018553
3		C91	Lymphoid leukaemia		85E
4		C92	Myeloid leukaemia		
5		C93	Monocytic leukaemia		on 2
6		C94	Other leukaemias of specified cell type		<u>≤</u>
,		C95	Leukaemia of unspecified cell type		March
8		C96	Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related		N
9 10		C90	tissue		2018.
11			Malignant neoplasms of independent		
12		C97	(primary) multiple sites		Down
13 14	Chronic renal disease	l12	Hypertensive renal disease		nloaded
15		I13	Hypertensive heart and renal disease		
16		N03	Chronic nephritic syndrome		Om
17		N04 N05	Nephrotic syndrome		h <u>t</u>
18			Unspecified nephritic syndrome Glomerular disorders in diseases classified		ф://
19 20		N08	elsewhere		b m jc
21		N18	Chronic kidney disease		p e e e e e e e e e e e e e e e e e e e
22		N19	Unspecified kidney failure		br.
23		Q60	Renal agenesis and other reduction defects of kidney		nj.cc
24		Q61	Cystic kidney disease		
25 26		Q62	Congenital obstructive defects of renal pelvis and congenital malformations of ureter		from http://bmjopen.bmj.com/ on April 9, 2024
27		Q63	Other congenital malformations of kidney		pril :
28 29		Q64	Other congenital malformations of urinary system		9, 20
30		Z94.0	Kidney transplant status		24
31		T80.9	Unspecified complication following infusion,	9999004	Renal dialysis
32		100.0	transfusion and therapeutic injection	0000004	complication
33		T00 0	Unspecified complication following infusion,	0040400	Dialysis 🤔
34		T80.9	transfusion and therapeutic injection	8842133	disequilibrium syndrome ୍ଦି
35 36			Unspecified complication following infusion,		Ċ
37		T80.9	transfusion and therapeutic injection	8842134	Dialysis hypertension
38		T80.9	Unspecified complication following infusion,	8842132	Dialysis diffigulty
39		100.8	transfusion and therapeutic injection	00 1 2 102	Dialysis diffigulty
40		T82.7	Infection and inflammatory reaction due to	8845140	Dialysis shimt
41			other cardiac and vascular devices, implants		infection 을
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43					

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				Pen	_
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				17-	
		and marks		018	
		and grafts Mechanical complication of other cardiac and		์ บั	
	T82.5	vascular devices and implants	8845141	Dialysis shugnt failure	
		Infection and inflammatory reaction due to		N	
	T82.7	other cardiac and vascular devices, implants	8847235	Dialysis shart virtual	
		and grafts		aneurysm ਨੂੰ	
		Other specified complications of cardiac and		N Dialveis shift	
	T82.8	vascular prosthetic devices, implants and	8844085	Dialysis shught stenosis	
		grafts		\mathcal{G}	1
	T02 0	Other specified complications of cardiac and	0044007	Dialysis shight	
	T82.8	vascular prosthetic devices, implants and grafts	8844087	arteriovenogs	1
		Other specified complications of cardiac and		aneurysm ದ	
	T82.8	vascular prosthetic devices, implants and	8844088	Dialysis shught	1
	• • • •	grafts	••••	obstruction	
		Other specified complications of cardiac and		Dialysia shuat	
	T82.8	vascular prosthetic devices, implants and	8844086	Dialysis shunt venous hypertension	
		grafts		Venous hypertension	
Organ	T86	Complications of transplanted organs and		Per la companya di managana di	
tranchiantation		4.			
transplantation		tissue		n.bn	
	Z94	tissue Transplanted organ and tissue status	4	Traumatic 9	
Cerebrospinal	Z94	Transplanted organ and tissue status	3498002	Traumatic g	
·			3498002	Traumatic g cerebrospinal fluid otorrhoea 9	
Cerebrospinal	Z94	Transplanted organ and tissue status	3498002	cerebrospinal fluid	
Cerebrospinal	Z94	Transplanted organ and tissue status	3498002 3498003	cerebrospinal fluid otorrhoea 일 Traumatic 골 cerebrospinal fluid	
Cerebrospinal	X94 S06.8 S06.8	Transplanted organ and tissue status Other intracranial injuries Other intracranial injuries	3498003	cerebrospinal fluid otorrhoea 의 Traumatic 공 cerebrospinal fluid rhinorrhoea	
Cerebrospinal	Z94 S06.8	Transplanted organ and tissue status Other intracranial injuries		cerebrospinal fluid otorrhoea	
Cerebrospinal	X94 S06.8 S06.8	Transplanted organ and tissue status Other intracranial injuries Other intracranial injuries	3498003	cerebrospinal fluid otorrhoea	
Cerebrospinal	Z94 S06.8 S06.8 G96.0	Transplanted organ and tissue status Other intracranial injuries Other intracranial injuries Cerebrospinal fluid leak	3498003 3498007	cerebrospinal fluid otorrhoea 9 Traumatic 3 cerebrospinal fluid rhinorrhoea 9 Spinal leakage Cerebrospinal fluid otorrhoea 9	
Cerebrospinal	X94 S06.8 S06.8 G96.0 G96.0	Transplanted organ and tissue status Other intracranial injuries Other intracranial injuries Cerebrospinal fluid leak Cerebrospinal fluid leak	3498003 3498007 8847107	cerebrospinal fluid otorrhoea S Traumatic A cerebrospinal fluid rhinorrhoea Spinal leakæge Cerebrospinal fluid otorrhoea Open traumætic	
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Cerebrospinal	Z94 S06.8 S06.8 G96.0 G96.0 S06.8	Transplanted organ and tissue status Other intracranial injuries Other intracranial injuries Cerebrospinal fluid leak Cerebrospinal fluid leak Other intracranial injuries	3498003 3498007 8847107 8843154	cerebrospinal fluid otorrhoea 9 Traumatic 5 cerebrospinal fluid rhinorrhoea 9 Spinal leakæge Cerebrospinal fluid otorrhoea 9 Open traumatic cerebrospinal fluid otorrhoea 9 Open traumatic cerebrospinal fluid otorrhoea 9 Open traumatic cerebrospinal fluid	
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Cerebrospinal	Z94 S06.8 S06.8 G96.0 G96.0 S06.8	Transplanted organ and tissue status Other intracranial injuries Other intracranial injuries Cerebrospinal fluid leak Cerebrospinal fluid leak Other intracranial injuries	3498003 3498007 8847107 8843154	cerebrospinal fluid otorrhoea 9 Traumatic 5 cerebrospinal fluid rhinorrhoea 5 Spinal leakæge Cerebrospinal fluid otorrhoea 6 Open traumatic cerebrospinal fluid otorrhoea 7 Open traumatic cerebrospinal fluid rhinorrhoea 6 Traumatic cerebrospinal fluid rhinorrhoea 6 Traumatic cerebrospinal fluid	
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Cerebrospinal	Z94 S06.8 S06.8 G96.0 G96.0 S06.8	Transplanted organ and tissue status Other intracranial injuries Other intracranial injuries Cerebrospinal fluid leak Cerebrospinal fluid leak Other intracranial injuries Other intracranial injuries	3498003 3498007 8847107 8843154 8843155	cerebrospinal fluid otorrhoea 9 Traumatic 5 cerebrospinal fluid rhinorrhoea 9 Spinal leakæge Cerebrospinal fluid otorrhoea 9 Open traumatic cerebrospinal fluid otorrhoea 9 Open traumatic cerebrospinal fluid otorrhoea 9 Open traumatic cerebrospinal fluid	

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1						2017					
2						7-O,					
3					c	cerebrospinal fluid					
4						hinorrhoea∞					
5					T	Fraumatic ^S					
6		S06.8	Other intracranial injuries	8843259	C	cerebrospin ll fluid					
7						otorrhoea 🚉					
8						Fraumatic ⊖					
9		S06.8	Other intracranial injuries	8843260		cerebrospir [2] fluid					
10						hinorrhoea∞					
11		000.0	0.11	0040504		Closed traugnatic					
12		S06.8	Other intracranial injuries	8843531		cerebrosping fluid					
13						otorrhoea ਨੂੰ					
14		S06.8	Other intracranial injuries	8843532		Closed traumatic					
15		300.6	Other intracramar injuries	0043332		cerebrospir <u>ନ</u> ୍ତ୍ରା hinorrhoeaବ୍ରି					
16		G96.0	Cerebrospinal fluid leak	3498021		Spinal leakage					
17						Cerebrospinal fluid					
18		G96.0	Cerebrospinal fluid leak	8847240		eakage					
19						Cerebrospinal fluid					
20		G97.0	Cerebrospinal fluid leak from spinal puncture	8836019		eak from spinal					
21						ouncture					
22 -	Invasive				j	nvasive <u>3</u>					
23	pneumococcal	A49.1	Streptococcal infection, unspecified site	8847765		oneumococ <mark>@</mark> al					
24	disease					nfection 3					
25 26		G00.1	Pneumococcal meningitis	3201001		Pneumoco & al					
26 27		000.1	1 Houristoodal Moningrillo	0201001		neningitis ≱					
28		A40.3	Sepsis due to Streptococcus pneumoniae	8838800		Pneumococcal					
29			·		S	sepsis 9, 202			Ctrontogogg		
30		A49.9	Bacterial infection, unspecified	7907001	E	Racteraemi le	and	A49.1	Streptococcal infection,	8847809	Pneumococcal
31		A43.3	bacterial infection, unspecified	7907001	L	Bacteraemi à	and	A49.1	unspecified site	0047009	infection
32						ugu			Streptococcal		
33		A41.9	Sepsis, unspecified	0389004	Ş	Sepsis :	and	A49.1	infection,	8847809	Pneumococcal
34							5.1.5	71.0	unspecified site		infection
35			Pactorial maninggoneshalitic and		F	ু Purulent ce			Streptococcal		Pneumococcal
36		G04.2	Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified	8831417		→	and	A49.1	infection,	8847809	infection
37			meningornyends, not elsewhere diassilled		ſ	meningitis 👨			unspecified site		HIECHOII
38						by c			Streptococcal		Pneumococcal
39		G03.9	Meningitis, unspecified	3229007	N	Meningitis မွိ	and	A49.1	infection,	8847809	infection
40		004.0	Frankalitia maralitia and annakatan 199	2020222		.4a.la.ma.a.m.'≘.	a.al	A 40 4	unspecified site	0047000	
41		G04.9	Encephalitis, myelitis and encephalomyelitis,	3239028	N	Myelomenipgitis	and	A49.1	Streptococcal	8847809	Pneumococcal
42											
42											

				17-0					
		unspecified		17-018553 on			infection, unspecified site		infection
	133.0	Acute and subacute infective endocarditis	8838820	Septic endocarditis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	I30.1	Infective pericarditis	8838821	ਤ Septic periderditis ਕੁੰ	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	J20.9	Acute bronchitis, unspecified	8838818	Septic bronghitis	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	J18.9	Pneumonia, unspecified	8838823	କ୍ଷ୍ମି Septic pneumonia ଟ୍ରି	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	A49.9	Bacterial infection, unspecified	0389014	Transient bacteraemia	and	A49.1		8847809	Pneumococcal infection
	A49.9	Bacterial infection, unspecified	0389015 0389016	Intermittento bacteraemia	and A49	A49.1		8847809	Pneumococcal infection
	A49.9	Bacterial infection, unspecified		Persistent bacteraemia	and	A49.1		8847809	Pneumococcal infection
	A49.9	Bacterial infection, unspecified	7907001	On Bacteraemi ≱ Orii o	and	A49.1		8847809	Pneumococcal infection
	A41.9	Sepsis, unspecified organism		9, 2024 by	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	M86.9	Osteomyelitis, unspecified	8838819	Septic oste	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
	A41.8	Other specified sepsis	8847009	Gram-positige bacterial se	and	A49.1	Streptococcal infection, unspecified site	8847809	Pneumococcal infection
Pneumococcal pneumonia	J13	Pneumonia due to Streptococcus pneumoniae	8838802	Pneumoco&al pneumonia			1		
•	J20.2	Acute bronchitis due to streptococcus	8838798	Pneumoco⊛al bronchitis ≦.					
	J15.9	Bacterial pneumonia, unspecified	4829003	Bacterial preumonia	and	A49.1	Streptococcal	8847809	Pneumococcal

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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	P2 Abstract		
		of what was done and what was found			
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		Zamo special seguent s			
Study design	4	Present key elements of study design early in the paper	P2-P5		
Setting Setting	5	Describe the setting, locations, and relevant dates, including	P5-P8		
Setting	3	periods of recruitment, exposure, follow-up, and data collection	1310		
Participants	6	(a) Give the eligibility criteria, and the sources and methods of	P6 Study design		
		selection of participants. Describe methods of follow-up	and population		
		(b) For matched studies, give matching criteria and number of	P6 Study design		
		exposed and unexposed	and population		
Variables	7	Clearly define all outcomes, exposures, predictors, potential	P6-P7 Study		
· · · · · · · · · · · · · · · · · · ·	,	confounders, and effect modifiers. Give diagnostic criteria, if applicable	variables		
Data sources/	8*	For each variable of interest, give sources of data and details of	P5 Data source		
measurement		methods of assessment (measurement). Describe comparability of			
		assessment methods if there is more than one group			
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	11	Explain how quantitative variables were handled in the analyses. If	P6-P7 Study		
variables		applicable, describe which groupings were chosen and why	variables		
Statistical methods	12	(a) Describe all statistical methods, including those used to control	P7-P8 Statistica		
		for confounding	analysis		
		(b) Describe any methods used to examine subgroups and	Not applicable		
		interactions			
		(c) Explain how missing data were addressed	P7 Study		
			variables		
		(d) If applicable, explain how loss to follow-up was addressed	P7 Study		
			variables		
		(\underline{e}) Describe any sensitivity analyses	Not applicable		
Results					
Participants	13*	(a) Report numbers of individuals at each stage of study—eg	P8		
-		numbers potentially eligible, examined for eligibility, confirmed	Characteristics		
		eligible, included in the study, completing follow-up, and analysed	of the study		
			population		
		(b) Give reasons for non-participation at each stage	Not applicable		
		(b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Not applicable Not applicable		
Descriptive data	14*				

		confounders	of the study
			population
		(b) Indicate number of participants with missing data for each	P8
		variable of interest	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	P8-10
		time	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-	P8-10
		adjusted estimates and their precision (eg, 95% confidence	
		interval). Make clear which confounders were adjusted for and	
		why they were included	
		(b) Report category boundaries when continuous variables were	P8-10
		categorized	
		(c) If relevant, consider translating estimates of relative risk into	Not applicable
		absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and	P8-10
		interactions, and sensitivity analyses	
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	P11-12
		potential bias or imprecision. Discuss both direction and magnitude	Limitation
		of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering	P10-12
		objectives, limitations, multiplicity of analyses, results from	
		similar studies, and other relevant evidence	
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	P13 Funding
		present study and, if applicable, for the original study on which the	
		present article is based	

^{*}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.

BMJ Open

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

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Primary Subject Heading :	Infectious diseases
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1	Risk of pneumococcal diseases in adults with underlying medical conditions: a
2	retrospective, cohort study using two Japanese healthcare databases
3	
4	Kentaro Imai, ¹ Tanaz Petigara, ² Melvin A. Kohn, ² Kei Nakashima, ³ Masahiro Aoshima, ³
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ABSTRACT

31	Objectives: To quantify the risk of pneumococcal pneumonia (PP) and invasive
32	pneumococcal disease (IPD) in adults aged ≥19 years with underlying medical conditions
33	compared with healthy adults of the same age in Japan.
34	Design: An observational, retrospective, cohort study using two healthcare claims databases
35	in Japan: Japan Medical Data Center (JMDC) and Medical Data Vision (MDV) databases.
36	Participants: A total of 10.4 million individuals, representing 9.3 million person-years of
37	follow-up, were included in the analysis. Eleven medical conditions as well as PP and IPD
38	were identified by ICD-10 diagnostic codes and/or local disease codes used in Japan.
39	Primary outcome measures: Adjusted rate ratios (RRs) for PP and IPD in adults with a
40	medical condition vs. adults without any medical condition were calculated using multivariate
41	Poisson regression models with age and/or sex as covariates.
42	Results: In the JMDC and MDV databases, respectively, adults ≥19 years with a medical
43	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
44	with two or more medical conditions (PP: 11.6, 2.8; IPD: 18.7, 5.8), and
45	immunocompromised adults (PP: 12.9, 1.8; IPD: 29.7, 4.0) were at greater risk of PP and
46	IPD compared with their healthy counterparts. Adults aged between 50 and 64 years with an
47	underlying medical condition (PP rate: 38.6 to 212.1 per 100,000 person-years) had a higher
48	rate of PP than those aged ≥65 years without any condition (PP rate: 13.2 to 93.0 per
49	100,000 person-years).
50	Conclusions: Adults of all ages with an underlying medical condition are at greater risk of PF
51	and IPD compared with adults without any medical condition. This risk increases with the
52	number of underlying medical conditions. Our results support extending pneumococcal
53	vaccination to younger adults with an underlying medical condition, especially those aged
54	between 50 and 64 years.

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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. 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. 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. 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. Subjects in the MDV database can be lost to follow-up. Both databases have been used in multiple studies published in peer-reviewed journals.

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 Japan²⁸ 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 Adults¹⁴ 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. 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. 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, and interpretation of the data, c.

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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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Japan. Available from: http://www.iryohoken.go.jp/shinryohoshu/searchMenu/doSearchInputBp 29. Baxter R, Yee A, Aukes L, <i>et al.</i> Risk of underlying chronic medical conditions for invasive pneumococcal disease in adults. <i>Vaccine</i> 2016; 34 :4293–7. 30. Chiba N, Morozumi M, Shouji M, <i>et al.</i> Changes in capsule and drug resistance of	452	https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm?s_cid=mm6140a4_w
http://www.iryohoken.go.jp/shinryohoshu/searchMenu/doSearchInputBp 29. Baxter R, Yee A, Aukes L, <i>et al.</i> Risk of underlying chronic medical conditions for invasive pneumococcal disease in adults. <i>Vaccine</i> 2016; 34 :4293–7. 30. Chiba N, Morozumi M, Shouji M, <i>et al.</i> Changes in capsule and drug resistance of	453	28. Various Information of Medical Fee, operated by Ministry of Health, Labour and Welfare
29. Baxter R, Yee A, Aukes L, <i>et al.</i> Risk of underlying chronic medical conditions for invasive pneumococcal disease in adults. <i>Vaccine</i> 2016; 34 :4293–7. 30. Chiba N, Morozumi M, Shouji M, <i>et al.</i> Changes in capsule and drug resistance of	454	Japan. Available from:
invasive pneumococcal disease in adults. <i>Vaccine</i> 2016; 34 :4293–7. 30. Chiba N, Morozumi M, Shouji M, <i>et al.</i> Changes in capsule and drug resistance of	455	http://www.iryohoken.go.jp/shinryohoshu/searchMenu/doSearchInputBp
30. Chiba N, Morozumi M, Shouji M, <i>et al</i> . Changes in capsule and drug resistance of	456	29. Baxter R, Yee A, Aukes L, et al. Risk of underlying chronic medical conditions for
	457	invasive pneumococcal disease in adults. Vaccine 2016;34:4293-7.
Pneumococci after introduction of PCV7, Japan, 2010-2013. Emerg Infect Dis 2014;20:1132–9.	458	30. Chiba N, Morozumi M, Shouji M, et al. Changes in capsule and drug resistance of
460 2014; 20 :1132–9.	459	Pneumococci after introduction of PCV7, Japan, 2010-2013. Emerg Infect Dis
	460	2014; 20 :1132–9.

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

					a MDV					
		JME								
	Cumulative	, , , , , , , , , , , , , , , , , , ,		IPD	Cumulative	Person-years (1)		PP	IPD	
	number of		%	Events	Events	number of	201	%	Events	Events
	adults					adults	∞			
Overall	7,433,221	6,721,329	100	840	80	2,967,475	2,565,033	100	2,569	117
Age				1			Š			
19–49 years old	5,744,222	5,211,057	78	433	28	566,908	47 ₹ ,300	18	117	7
50-64 years old	1,522,054	1,368,055	20	296	45	776,809	67\$365	27	318	26
≥65 years old ⁽²⁾	166,945	142,218	2	111	7	1,623,758	1,41 5 ,368	55	2,134	84
Sex							fo			
Female	3,326,903	2,957,528	44	327	20	1,620,634	1,39 4 ,668	54	1,109	61
Male	4,106,318	3,763,802	56	513	60	1,346,841	1,17,364	46	1,460	56
Risk status ⁽²⁾							:/ <u>}</u>			
Healthy (no condition)	6,603,349	5,975,767	89	436	33	1,494,204	1,24 <mark>2</mark> ,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 Medical conditions ⁽³⁾	128,966	113,909	2	154	28	628,565	55 <mark>6</mark> ,208	22	752	48
Medical conditions ⁽³⁾							bn			
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	473,870	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	54 D ,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	10\$\overline{\ove	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	্ট্ 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	ر <u>ه</u> ,031	0.2	26	1
Organ transplantation	2,525	2,214	0.03	17	16	3,895	§ ,535	0.1	21	2
Cerebrospinal fluid leakage	298	264	0.004	0	0	355	<u>∵</u> 318	0.01	0	0
Number of conditions							Pro			
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	58 5 ,730	23	1,238	71
		, -		I		,	ا ن ن ت		,	

⁽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 personnia

- (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.



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

		All ages	Age subgroups						
		19 years old ⁽²⁾)	19	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% CIR	Rate ⁽³⁾	RR ⁽⁵⁾ (95% CI)	
Overall	12.5		8.3		21.6	8. [78.0		
Risk status						Ои			
Healthy (no condition)	7.3	1.0	6.3	1.0	11.5	1.0 nlo	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⁾						om.			
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						m/ «			
0	7.3	1.0	6.3	1.0	11.5	1.0 yn /	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) <u>9</u>	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)	

^{| 22 | 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

		years old)	19-	-49 years old	Age subgroups		≥65 years old	
	Rate ⁽²⁾	RR ⁽³⁾ (95% CI)	Rate ⁽²⁾	Rate ⁽²⁾ RR ⁽⁴⁾ (95% CI)		RR ⁽⁴⁾ (95% CI) ♀	Rate ⁽²⁾	RR ⁽⁴⁾ (95% CI)
Overall	100.2		24.9		46.8	8. [150.8	
Risk status						Оом		
Healthy (no condition)	55.6	1.0	17.8	1.0	30.2	1.0 nl	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⁾						rom		
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) 8	165.5	1.7 (1.5–1.9)
Number of conditions						m/ .		
0	55.6	1.0	17.8	1.0	30.2	1.0 on /	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) ថ្មី	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) ,9	257.9	2.7 (2.4–3.0)

^{| 22 | 211.4 | 2.8 (2.5–3.0) | 75.4 | 4.2 (2.6–6.7) | 98.2 | 3.1 (2.4–4.0) \(\}triangle \) | 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

Programmed 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	Age subgroups থ							
	(≥	19 years old ⁽²⁾)	19	9–49 years old	50)–64 years old ⊖	≥6:	5 years old ⁽²⁾		
	Rate ⁽³⁾	RR ⁽⁴⁾ (95% CI)	Rate ⁽³⁾	RR ⁽⁵⁾ (95%CI)	Rate ⁽³⁾	RR ⁽⁵⁾ (95% 🛱)	Rate ⁽³⁾	RR ⁽⁵⁾ (95% CI)		
Overall	1.2		0.5		3.3	8. [4.9			
Risk status						Ow				
Healthy (no condition)	0.6	1.0	0.3	1.0	1.6	1.0 nlo	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.🕏	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 🖺)	22.7	14.9 (1.6–143)		
Medical condition ⁽¹⁾						om				
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🗿)	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 (5.5–195)	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.	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						D /				
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 (6.2–22.49)	22.7	8.2 (0.9–79.2)		

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

		All ages			Ag	e subgroups ≅		
	(≥1	19 years old)	19	–49 years old	50	–64 years old ⊖	≥6	65 years old
	Rate ⁽²⁾	RR ⁽³⁾ (95% CI)	Rate ⁽²⁾	RR ⁽⁴⁾ (95% CI)	Rate ⁽²⁾	RR ⁽⁴⁾ (95% 🛱)	Rate ⁽¹⁾	RR ⁽⁴⁾ (95% CI)
Overall	4.6		1.5		3.8	<u> </u>	5.9	
Risk status						Ow		
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 (2.7–31.4)	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. Ž)	9.2	3.1 (1.7–5.6)
Medical condition ⁽¹⁾						orr		
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🕏)	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😨)	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. <mark>9</mark>)	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 (3.1–763)	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						3		
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, 4)	11.9	4.1 (2.3–7.1)

Supplementary materials

Supplementary Figure 1. Study design

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

pneumonia

Supplementary tables

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

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

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

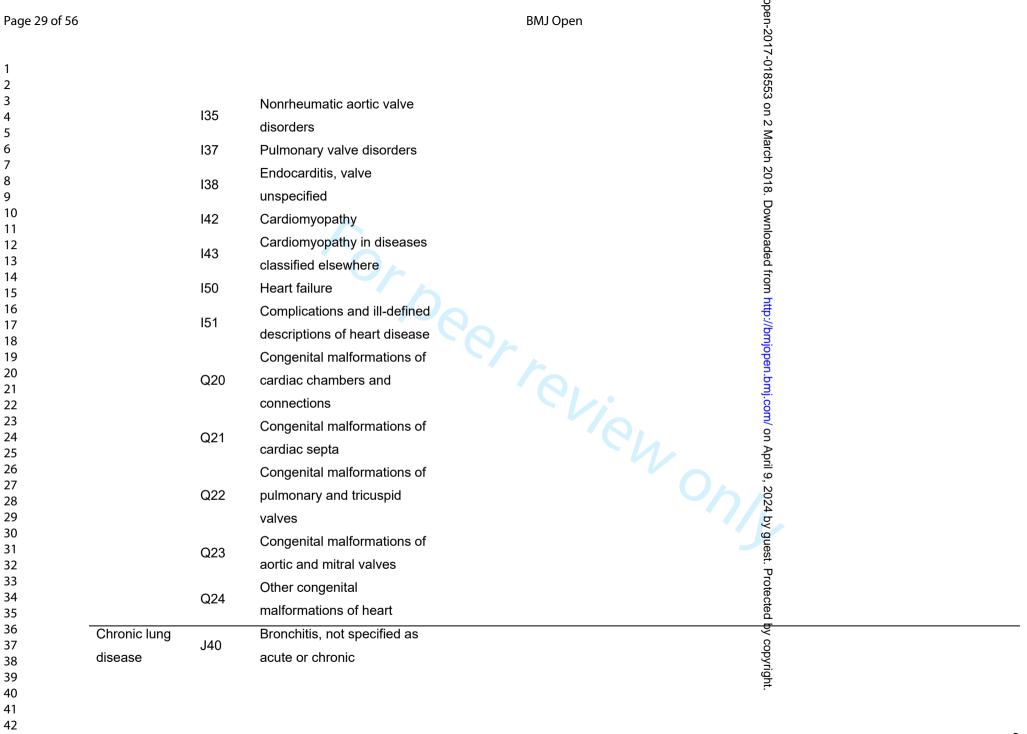
Supplementary Table 4. Rates and rate ratios of invasive pneumococcal diseases in the JMDC database

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

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

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Supplementary	Table 1.	International Classification of	Diseases, ve	rsion 10 Codes		118553 on 2		
Condition	ICD-10	Description	Disease	Description	ICD-	escription	Disease	Description
	codes		code		10	rch 2018.	code	
	(2015)		defined by		codes	018.	defined	
			MHLW		(2015)	Dow	by	
			Japan			/nloa	MHLW	
						ided	Japan	
Chronic heart	105	Rheumatic mitral valve				from		
disease	100	diseases				http		
	106	Rheumatic aortic valve)://bn		
		diseases				njope		
	107	Rheumatic tricuspid valve				en.br		
		diseases				nj.cc		
	108	Multiple valve diseases				om/ c		
	109	Other rheumatic heart				ŏ ≱		
		diseases				oril 9		
	I11.0	71				, 202		
		with (congestive) heart failure				24 by		
		Hypertensive heart and renal				/ gue		
	I13.0	disease with (congestive)				et. F		
		heart failure				rote		
		Hypertensive heart and renal				cted		
	I13.2	disease with both				by o		
		(congestive) heart failure and				сору		
		renal failure				Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.		

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122	infarction	າ 201
	Certain current complications	 D
123	following acute myocardial) Own
	infarction	load
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125.5	Ischemic cardiomyopathy	rii 9,
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105.0	Other forms of chronic	4 by
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J41	Simple and mucopurulent chronic bronchitis		3553 on 2
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J60	Coalworker pneumoconiosis		//bm/
J61	Pneumoconiosis due to asbestos and other mineral fibres		open-2017-018553 on 2 March 2018. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Prote
J62	Pneumoconiosis due to dust containing silica		n/ on Ap
J63	Pneumoconiosis due to other inorganic dusts		oril 9, 202
J64	Unspecified pneumoconiosis		4 by
J66	Airway disease due to specific organic dust		guest. P
J67	Hypersensitivity pneumonitis due to organic dust		
J84	Other interstitial pulmonary diseases		cted by copyright.
J96.1	Chronic respiratory failure		right.

Diabetes mellitus E10 Type 1 diabetes mellitus E11 Type 2 diabetes mellitus Chronic liver disease E13 Tother acute viral hepatitis (except Acute hepatitis C) B17.1 Tother acute viral hepatitis (except Acute hepatitis C) B18.1 Chronic viral hepatitis (except Acute hepatitis C) B19.9 Tother acute viral hepatitis (except Acute hepatitis C) B19.9 Tother acute viral hepatitis (except Acute hepatitis C) B19.9 Tother acute viral hepatitis (except Acute hepatitis C) B19.9 Tother acute viral hepatitis (except Acute hepatitis C) B19.9 Tother acute viral hepatitis (except Acute hepatitis C) B19.9 Tother acute viral hepatitis (except Acute hepatitis C) B19.9 Tother acute viral hepatitis (except Acute hepatitis (except Acute hepatitis C) B19.9 Tother acute viral hepatitis (except Acute hepatitis (except Acute hepatitis C) B19.9 Tother acute viral hepatitis (except Acute hepatitis (except Acute hepatitis C) B19.9 Tother acute viral hepatitis (except Acute hepatitis (e				0185
E84 Cystic fibrosis Pulmonary heart disease, unspecified Pulmonary heart disease Pulmonary heart di		J98	Other respiratory disorders	53 01
Diabetes mellitus		E84	Cystic fibrosis	7 2 7
Diabetes mellitus E11 Type 2 diabetes mellitus E12 Malnutrition-related diabetes mellitus E13 Other specified diabetes mellitus E14 Unspecified diabetes mellitus E15 Acute hepatitis B (except dela-agent and without hepatic coma) E17 (except B17.1) E18 Chronic viral hepatitis E19 Chronic viral hepatitis E19 (except H9.9) E29 Chronic viral hepatitis E20			Pulmonary heart disease,	// Aarc
Diabetes mellitus E10 Type 1 diabetes mellitus Type 2 diabetes mellitus E11 Type 2 diabetes mellitus E12 Malnutrition-related diabetes mellitus Malnutrition-related diabetes mellitus Type 2		127.9	unspecified	n 20
E11 Type 2 diabetes mellitus E12 Malnutrition-related diabetes mellitus E13 Other specified diabetes mellitus E14 Unspecified diabetes mellitus Acute hepatitis B (except Acute hepatitis B without delta-agent and without hepatic coma) E16 (except (except B17.1) E17 (except B17.1) E18 Chronic viral hepatitis (except Acute hepatitis C) E19 (except Acute hepatitis C) E19 (except Hospecified viral hepatitis (except Unspecified viral hepatitis without hepatic coma) E19 (except Hospecified viral hepatitis without hepatic coma) E19 (except Hospecified viral hepatitis without hepatic coma) E20 (Acute Hepatitis Without hepatic coma) E21 (Acute Hepatitis Without hepatic coma) E22 (Acute Hepatitis Without hepatic coma) E23 (Acute Hepatitis Without hepatic coma) E24 (Acute Hepatitis Without hepatic coma) E25 (Acute Hepatitis Without hepatic coma) E26 (Acute Hepatitis Without hepatic coma) E27 (Acute Hepatitis Without hepatic coma)		E10	Type 1 diabetes mellitus	18. Down
E12 Malnutrition-related diabetes mellitus E13 Other specified diabetes mellitus E14 Unspecified diabetes mellitus Chronic liver disease B16 (except disease) B17 (except B17.1) B18 Chronic viral hepatitis (except Acute hepatitis C) B18 Chronic viral hepatitis (except Acute hepatitis C) B19 (except B19.9) (except Acute hepatitis (except Acute hepatitis C) B18 Chronic viral hepatitis (except Acute hepatitis C) B19 (except Acute hepatitis C) B19 (except Acute hepatitis (except Acute hepatitis C) B19 (except Acute hepatitis C) B19 (except Acute hepatitis (except Acute hepatitis C) B19 (except Acute hepatitis C) B19 (except Acute hepatitis (except Unspecified viral hepatitis (except Unspecified viral hepatitis without hepatic coma) K70 Alcoholic liver disease		E11	Type 2 diabetes mellitus	ilo ad
mellitus E13 Other specified diabetes mellitus E14 Unspecified diabetes mellitus Chronic liver disease B16 Acute hepatitis B (except Acute hepatitis C) B17 (except B17.1) Chronic liver disease B17 (except B17.1) B18 Chronic viral hepatitis (except Acute hepatitis C) B19 (except H9.9) (except H9.9) (except H9.9) (except H9.9) K70 Alcoholic liver disease		E40	Malnutrition-related diabetes	ed fr
Chronic liver disease E13 Other specified diabetes mellitus E14 Unspecified diabetes mellitus Acute hepatitis B (except delta-agent and without hepatic coma) B17 (except B17.1) B18 Chronic viral hepatitis B17 (except B17.1) B18 Chronic viral hepatitis (except Hornic viral hepatitis (except Unspecified viral hepatitis without hepatic coma) K70 Alcoholic liver disease		E12	mellitus	rom
mellitus E14 Unspecified diabetes mellitus Acute hepatitis B (except Acute hepatitis B without delta-agent and without hepatic coma) B17 (except B17.1) B18 Chronic viral hepatitis C) B19 (except B19.9) (except B19.9) K70 Alcoholic liver disease		F12	Other specified diabetes	nttp:/
E14 Unspecified diabetes mellitus Chronic liver disease B16 Acute hepatitis B (except Acute hepatitis B without delta-agent and without hepatic coma)		EIS	mellitus	/bmj
Chronic liver disease B16		E14	Unspecified diabetes mellitus	oper
Chronic liver disease Acute hepatitis B without delta-agent and without hepatic coma		B16	Acute hepatitis B (except	Б Э
disease B16.9 delta-agent and without hepatic coma B17	Chronic liver		Acute hepatitis B without	
hepatic coma) B17 (except B17.1) B18 Chronic viral hepatitis Unspecified viral hepatitis (except Unspecified viral hepatitis (except Unspecified viral hepatitis without hepatic coma) K70 Alcoholic liver disease	disease		delta-agent and without	n/ or
Other acute viral hepatitis (except B17.1) B18 Chronic viral hepatitis Unspecified viral hepatitis (except Unspecified viral hepatitis Hepatitis without hepatic coma) K70 Alcoholic liver disease		D10.9)	hepatic coma)	1 Apr
(except B17.1) B18 Chronic viral hepatitis Unspecified viral hepatitis (except Unspecified viral hepatitis (except B19.9) K70 Alcoholic liver disease		B17	Other acute viral henatitis	≓: ⊙
B17.1) B18 Chronic viral hepatitis Unspecified viral hepatitis (except Unspecified viral hepatitis without hepatic coma) K70 Alcoholic liver disease		(except	(except Acute henatitis C)	2024
B18 Chronic viral hepatitis Unspecified viral hepatitis (except Unspecified viral hepatitis without hepatic coma) K70 Alcoholic liver disease		B17.1)	(except Acute Repatitis C)	by.
Unspecified viral hepatitis (except Unspecified viral hepatitis without hepatic coma) K70 Alcoholic liver disease		B18	Chronic viral hepatitis	gues
(except Unspecified viral hepatitis without hepatic coma) K70 Alcoholic liver disease		R10	Unspecified viral hepatitis	∷ P
hepatitis without hepatic B19.9) coma) K70 Alcoholic liver disease			(except Unspecified viral	otec
coma) K70 Alcoholic liver disease			hepatitis without hepatic	fe d
K70 Alcoholic liver disease		B 10.0)	coma)	у С
		K70	Alcoholic liver disease	эрyright.

			7-018553 on 2 March 2018. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.
	K71	Toxic liver disease (except	553 0
	(except	Toxic liver disease with	ñ 2
	K71.2)	hepatic necrosis)	Marc
	K72	Hepatic failure, not elsewhere	ћ 20
	(except	classified (except Acute and	148.
	K72.0)	subacute hepatic failure)	Dow
	,	Chronic hepatitis, not	nloa
	K73	elsewhere classified	de
	K74	Fibrosis and cirrhosis of liver	from
		Other inflammatory liver	http
	K75	diseases	://bm
	K76	Other diseases of liver	ojo pe
		Liver disorders in diseases	b b
	K77	diseases Other diseases of liver Liver disorders in diseases classified elsewhere	
Asplenia	D56	classified elsewhere Thalassaemia Sickle-cell disorders Acquired pure red cell aplasia [erythroblastopenia]	——————————————————————————————————————
	D57	Sickle-cell disorders	n Ap
	DCO	Acquired pure red cell aplasia	ī: 9
	D60	[erythroblastopenia]	202
	D61	Other aplastic anaemias	4 by
	D73.0	Hyposplenism	gue
	D73.1	Hypersplenism	st. P
	D73.8	Other diseases of spleen	rote
	000.0	Congenital malformations of	cted
	Q89.0	spleen	by c
	Q89.3	Situs inversus	оругі
Alcoholism	F10.2	Dependence syndrome	ight.

			91
		Human immunodeficiency	3 on
HIV infection	B20	virus [HIV] disease resulting	2 ≤
THV IIIIection	D20	in infectious and parasitic	arch
		diseases	201
		Human immunodeficiency	,© D
	B21	virus [HIV] disease resulting	own
		in malignant neoplasms	load
		Human immunodeficiency	ed fr
	B22	virus [HIV] disease resulting	mo,
		in other specified diseases	http:
		Human immunodeficiency	//bm
	B23	virus [HIV] disease resulting	jope
		in other conditions	n.bm
		Unspecified human	ıj.co
	B24	immunodeficiency virus [HIV]	m/ o
		in other conditions Unspecified human immunodeficiency virus [HIV] disease	53 on 2 March 2018. Downloaded from http://bmjopen.bmj.com/ on Apr l 9, 2024 by guest. Protected by copyright.
Cancer	C00	Malignant neoplasm of lip	9,
	C01	Malignant neoplasm of base	202
	CUT	of tongue	4 by
		Malignant neoplasm of other	gue
	C02	and unspecified parts of	st. P
		tongue	rote
	C03	Malignant neoplasm of gum	cted
	C04	Malignant neoplasm of floor	by c
	C04	of mouth	оруг
	C05	Malignant neoplasm of palate	ight.

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

		BMJ Open	ppen-201
			7-018
C18	Malignant neoplasm of colon		553 on
C19	Malignant neoplasm of rectosigmoid junction		2 Marc
C20	Malignant neoplasm of rectum		h 2018.
C21	Malignant neoplasm of anus		Downloa
C22	Malignant neoplasm of liver		aded fror
C23	and intrahepatic bile ducts Malignant neoplasm of gallbladder		n http://br
C24	Malignant neoplasm of other and unspecified parts of biliary tract		ppen-2017-018553 on 2 March 2018. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.
C25	Malignant neoplasm of pancreas		om/ on Ap
C26	Malignant neoplasm of other and ill-defined digestive organs		pril 9, 2024 by
C30	Malignant neoplasm of nasal cavity and middle ear		guest. I
C31	Malignant neoplasm of accessory sinuses		^o rotecte:
C32	Malignant neoplasm of larynx		d by c
C33	Malignant neoplasm of trachea		opyright.

		BMJ Open	ppen-2017-018553 on 2 March 2018. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.
			7-01855
C34	Malignant neoplasm of		53 on 2
	bronchus and lung		2 Mai
C37	Malignant neoplasm of thymus		rch 20
C38	Malignant neoplasm of heart,)18. D
C36	mediastinum and pleura		own
	Malignant neoplasm of other		oade
C39	and ill-defined sites in the		₃d frc
	respiratory system and		m ⊒
	intrathoracic organs		тф://
	Malignant neoplasm of bone		omjo
C40	and articular cartilage of		pen.
	limbs		bmj.
044	Malignant neoplasm of bone		com/
C41	and articular cartilage of other		on /
C43	and unspecified sites		April
C43	Malignant melanoma of skin Other malignant neoplasms		9, 20
C44	of skin)24 k
C45	Mesothelioma		у дс
C46	Kaposi sarcoma		lest.
0.10	Malignant neoplasm of		Prot
C47	peripheral nerves and		ecte
-	autonomic nervous system		d by
	,		сору
			right
			•

		BMJ Open	ppen-2017-018553 on 2 March 2018. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.
			-018553
	Malignant neoplasm of		on
C48	retroperitoneum and		2 Ma
	peritoneum		arch
C49	Malignant neoplasm of other		201
0.0	connective and soft tissue		8. D
C50	Malignant neoplasm of breast		ownl
C51	Malignant neoplasm of vulva		oade
C52	Malignant neoplasm of		ed fr
002	vagina		m
C53	Malignant neoplasm of cervix		ıttp:/
000	uteri		/bmj
C54	Malignant neoplasm of		oper
004	corpus uteri		ı.bm
C55	Malignant neoplasm of		j.cor
033	uterus, part unspecified		n/ or
C56	Malignant neoplasm of ovary		٦ Ap
	Malignant neoplasm of other		rii 9,
C57	and unspecified female		202
	genital organs		4 by
CEO	Malignant neoplasm of		gue
C58	placenta		st. P
C60	Malignant neoplasm of penis		rote
004	Malignant neoplasm of		cted
C61	prostate		by c
C62	Malignant neoplasm of testis		юру
			ight.

	BMJ Open	ppen-2017
	Malignant neoplasm of other	ppen-2017-018553 on 2 March 2018. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.
C63	and unspecified male genital organs	2 March
C64	Malignant neoplasm of kidney, except renal pelvis	2018. Do
C65	Malignant neoplasm of renal pelvis	ownloade
C66	Malignant neoplasm of ureter	ed fr
C67	Malignant neoplasm of bladder	om http://t
C68	bladder Malignant neoplasm of other and unspecified urinary organs Malignant neoplasm of eye and adnexa Malignant neoplasm of meninges Malignant neoplasm of brain Malignant neoplasm of spinal	bmjopen.b
C69	Malignant neoplasm of eye and adnexa	mj.com/ oı
C70	Malignant neoplasm of meninges	า April 9,
C71	Malignant neoplasm of brain	202
	Malignant neoplasm of spinal	4 by
C72	cord, cranial nerves and other	gue
012	parts of central nervous	st. P
	system	rotec
C73	Malignant neoplasm of	ted
010	thyroid gland	by co
C74	Malignant neoplasm of	opyrig
	adrenal gland	Ħ.

		BMJ Open	ppen-2017-018553 on 2 March 2018. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright.
			17-01
			18553
	Malignant neoplasm of other		3 on
C75	endocrine glands and related		2 M ₂
	structures		arch
C76	Malignant neoplasm of other		201
0,0	and ill-defined sites		8. D
	Secondary and unspecified		ownl
C77	malignant neoplasm of lymph		oade
	nodes		ed fr
	Secondary malignant		om <mark>t</mark>
C78	neoplasm of respiratory and		ıttp:/
	digestive organs		/bmj
	Secondary malignant		oper
C79	neoplasm of other and		1.bm
	unspecified sites		j.con
C80	Malignant neoplasm, without		n⁄ or
000	specification of site		ו Api
C81	Hodgkin lymphoma		≟ 9,
C82	Follicular lymphoma		202
C83	Non-follicular lymphoma		4 by
C84	Mature T/NK-cell lymphomas		gue
C85	Other and unspecified types		st. P
C03	of non-Hodgkin lymphoma		rote
C86	Other specified types of		cted
C00	T/NK-cell lymphoma		by c
C88	Malignant		opyr
C00	immunoproliferative diseases		ight.

			7-018553 on 2 March 2018. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Protected by copyright
		Multiple myeloma and	53 or
	C90	malignant plasma cell	1 2 V
		neoplasms	1arch
	C91	Lymphoid leukaemia	1 20
	C92	Myeloid leukaemia	
	C93	Monocytic leukaemia	own
	C04	Other leukaemias of specified	load
	C94	cell type	ed fi
	COF	Leukaemia of unspecified cell	mo ⁻
	C95	type	http:
		Other and unspecified	//bm
	COG	malignant neoplasms of	jope
	C96	lymphoid, haematopoietic	n.bm
		and related tissue	J. CO
		Malignant neoplasms of	س/ OI
	C97	independent (primary)	n Ap
		type Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissue Malignant neoplasms of independent (primary) multiple sites	ril 9,
Chronic renal	l12	Hypertensive renal disease	202
disease	112	Hypertensive renal disease	4 by
	l13	Hypertensive heart and renal	gue
	113	disease	st. P
	N03	Chronic nephritic syndrome	rote
	N04	Nephrotic syndrome	cted
	NOE	Unspecified nephritic	by c
	N05	syndrome	юруі
			right

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N08	Glomerular disorders in			
INUO	diseases classified elsewhere			
N18	Chronic kidney disease			
N19	Unspecified kidney failure			
Q60	Renal agenesis and other			
Qou	reduction defects of kidney			
Q61	Cystic kidney disease			
	Congenital obstructive			
Q62	defects of renal pelvis and			
Q02	congenital malformations of			
	ureter		Renal dialysis complication	
Q63	Other congenital			
QUS	malformations of kidney			
	Other congenital			
Q64	malformations of urinary			
	system			
Z94.0	Kidney transplant status			
	Unspecified complication		Renal dialysis	
T80.9	following infusion, transfusion	9999004	complication	
	and therapeutic injection		Complication	
	Unspecified complication		Dialysis	
T80.9	following infusion, transfusion	8842133	disequilibrium	
	and therapeutic injection		syndrome	
T80.9	Unspecified complication		Dialysis	
	following infusion, transfusion	8842134	hypotension	
	and therapeutic injection		пурованыш	

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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	O 10000 OIL & MIGIGIL &OIL
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 Traumatic	Downloaded Hall Indexion being on the state of body in St.
	S06.8	Other intracranial injuries	3498003	cerebrospinal fluid	91. 91. 91. 91. 91. 91. 91. 91. 91. 91.
	G96.0	Cerebrospinal fluid leak	3498007	Spinal leakage	9
	G96.0	Cerebrospinal fluid leak	8847107	Cerebrospinal fluid otorrhoea	
	S06.8	Other intracranial injuries	8843154	Open traumatic cerebrospinal fluid otorrhoea	oz r vy gud
	S06.8	Other intracranial injuries	8843155	Open traumatic cerebrospinal fluid rhinorrhoea	ö: - Oacac
	S06.8	Other intracranial injuries	8843261	Traumatic cerebrospinal fluid otorrhoea	у сорупции.

					018553 on 2 March 2018. Downloaded from http://bmjopen.bmj.com/ on April 9, 2024 by guest. Pr <mark>otected by copyright</mark>
				Traumatic	3 on
	S06.8	Other intracranial injuries	8843262	cerebrospinal fluid	2 ≤
				rhinorrhoea	arch
				Traumatic	201
	S06.8	Other intracranial injuries	8843259	cerebrospinal fluid	8. D
				otorrhoea	own
				Traumatic	loade
	S06.8	Other intracranial injuries	8843260	cerebrospinal fluid	ed fr
				rhinorrhoea	om
				Closed traumatic	ttp:/
	S06.8	Other intracranial injuries	8843531	cerebrospinal fluid	/bmj
				otorrhoea	oper
				Closed traumatic	1.bm
	S06.8	Other intracranial injuries	8843532	cerebrospinal	j.con
				rhinorrhoea	n∕ or
	G96.0	Cerebrospinal fluid leak	3498021	Spinal leakage	1 Apr
	G96.0	Cerebrospinal fluid leak Cerebrospinal fluid leak from	8847240	Cerebrospinal fluid	ii 9,
			0041240	leakage	202,
				Cerebrospinal fluid	4 by
	G97.0	spinal puncture	8836019	leak from spinal	gues
		opinal pariotaro		puncture	; ;
Invasive		Streptococcal infection,		Invasive	otec
pneumococcal	A49.1	unspecified site	8847765	pneumococcal	ted -
disease		unspecified site		infection	бу с
	G00.1	Pneumococcal meningitis	3201001	Pneumococcal	opyri
	3 00.1	amooooai momigiao	3201001	meningitis	ght.

A40.3	Sepsis due to Streptococcus pneumoniae	8838800	Pneumococcal sepsis			8553 on 2 Mastreptococcal		
A49.9	Bacterial infection, unspecified	7907001	Bacteraemia	and	A49.1	Marketion, which was pecified site	8847809	Pneumococcal infection
A41.9	Sepsis, unspecified	0389004	Sepsis	and	A49.1	Enspecified	8847809	Pneumococcal infection
G04.2	Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified	8831417	Purulent cerebral meningitis	and	A49.1	Streptococcal infection, inspecified site	8847809	Pneumococcal infection
G03.9	Meningitis, unspecified	3229007	Meningitis	and	A49.1	Streptococcal Infection, Pilinspecified Streptococcal	8847809	Pneumococcal infection
G04.9	Encephalitis, myelitis and encephalomyelitis, unspecified	3239028	Myelomeningitis	and	A49.1	Streptococcal fifection, unspecified site	8847809	Pneumococcal infection
133.0	Acute and subacute infective endocarditis	8838820	Septic endocarditis	and	A49.1	Etreptococcal Infection, Co Inspecified Etite	8847809	Pneumococcal infection

l30.1	Infective pericarditis	8838821	Septic pericarditis	and	A49.1	Streptococcal Streptococcal Menspecified Ste	8847809	Pneumococcal infection
J20.9	Acute bronchitis, unspecified	8838818	Septic bronchitis	and	A49.1	treptococcal of the street of	8847809	Pneumococcal infection
J18.9	Pneumonia, unspecified	8838823	Septic pneumonia	and	A49.1	Streptococcal tinfection, linspecified	8847809	Pneumococcal infection
A49.9	Bacterial infection, unspecified	0389014	Transient bacteraemia	and	A49.1	infection, inspecified inspecified	8847809	Pneumococcal infection
A49.9	Bacterial infection, unspecified	0389015	Intermittent bacteraemia	and	A49.1	Streptococcal Exprection, Unspecified	8847809	Pneumococcal infection
A49.9	Bacterial infection, unspecified	0389016	Persistent bacteraemia	and	A49.1	Streptococcal fection, grant fection, grant fection, grant fection, grant feet feet feet feet feet feet feet fe	8847809	Pneumococcal infection
A49.9	Bacterial infection, unspecified	7907001	Bacteraemia	and	A49.1	streptococcal	8847809	Pneumococcal infection

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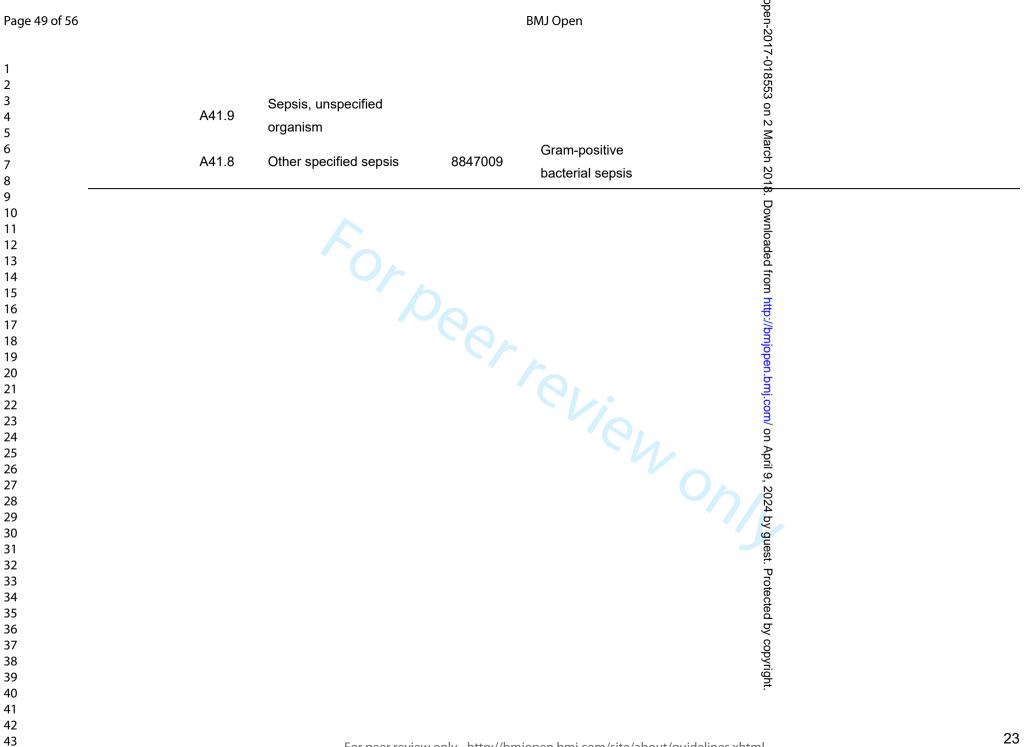
38

39 40

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J18	Pneumonia, organism unspecified	4860030	Pneumonia	and	A49.1	Streptococcal Magnspecified Attention, Streptococcal	8847809	Pneumococcal infection
J86	Pyothorax			and	A49.1	Streptococcal Enfection, anspecified Site	8847809	Pneumococcal infection
J90	Pleural effusion, not elsewhere classified			and	A49.1	streptococcal infection, unspecified	8847809	Pneumococcal infection
J91	Pleural effusion in other conditions classified elsewhere			and	A49.1	infection, inspecified inspecified inspecified	8847809	Pneumococcal infection
Exclusion criteria (belov						9, 2		
A49.9	Bacterial infection, unspecified	7907001	Bacteraemia			.024 by		
A49.9	Bacterial infection,	0389014	Transient bacteraemia			guest		
	unspecified Bacterial infection,		Intermittent			Prot		
A49.9	unspecified	0389015	bacteraemia			ected		
A49.9	Bacterial infection,	0389016	Persistent			by c		
A49.9	unspecified	0000010	bacteraemia			e April 9, 2024 by guest. Protected by copyright.		



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

		Pre-PCV era	Posta					
		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	8. [15.6			
Risk status) Ow				
Healthy (no condition)	5.5	1.0	8.7	1.0 항	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⁾				ă				
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				on ,				
0	5.5	1.0	8.7	1.0 Pr	7.7	1.0		
1	18.5	3.0 (1.9–4.5)	27.7	2.7 (2.0–3.7) $\overline{\mathfrak{G}}$	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, organitransplantation, 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. Rate	es and rate ratios		MJ Open monia in the	MDV database		
	Pr	e-PCV era		Post	PCV era	
	2	009–2010		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			
Risk status				C		
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)		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) 2.4 (2.0–3.0)	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)		1.6 (1.4–1.8)
Number of conditions				· CII		
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)		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, organgiransplantation, 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

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⁽³⁾ Age-and-sex-adjusted rate ratio

		Pre-PCV era	Post- CV era					
		2006–2010 ⁽²⁾		2011–2012 ⁽²⁾	1	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	8.	1.4			
Risk status				90w				
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	h	42.2	44.8 (20.0–100.1)	24.8	32.1 (13.0–79.2)		
Medical condition ⁽¹⁾				ä				
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				on				
0	0.3	1.0	0.7	1.0 ਊ	0.7	1.0		
1	1.3	2.3 (0.5–11.4)	2.6	3.2 (1.5–6.9) $\overline{\wp}$	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, organitransplantation, 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

	F	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	8. [4.8			
Risk status				WO				
Healthy (no condition)	3.4	1.0	1.8	1.0 nd	2.7	1.0		
At-risk conditions	4.2	0.8 (0.3–2.4)	6.7	3.0 (1.8–5.2)ត្តិ	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⁾				m				
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				on				
0	3.4	1.0	1.8	1.0 ਊ	2.7	1.0		
1	3.8	0.8 (0.3–2.6)	2.2	1.1 (0.5–2.4), <u>o</u>	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) ^N	13.8	5.3 (3.5–7.9)		

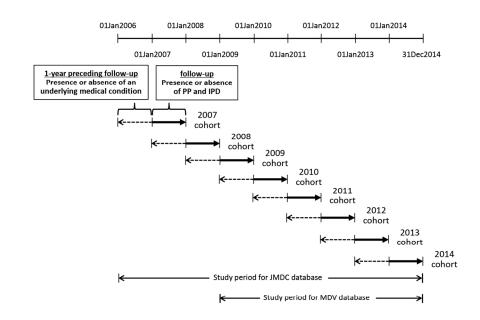
 ⁽¹⁾ Results of subgroups with other medical conditions, including HIV/AIDS, alcoholism, asplenia, organitransplantation, and cerebrospinal fluid leakage, are not shown.
 (2) Per 100,000 person-years
 (3) Age-and-sex-adjusted rate ratio

Abbreviations: CI, confidence interval; MDV, Medical Data Vision; PCV, pneumococcal conjugate vaccine; RR, rate ratio

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⁽³⁾ Age-and-sex-adjusted rate ratio

Supplementary Figure 1.



127x95mm (300 x 300 DPI)

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	P1 Title
		title or the abstract	
		(b) Provide in the abstract an informative and balanced summary	P2 Abstract
		of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the	P4-P5
		investigation being reported	
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	P5-P8
		periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of	P6 Study design
		selection of participants. Describe methods of follow-up	and population
		(b) For matched studies, give matching criteria and number of	P6 Study design
		exposed and unexposed	and population
Variables	7	Clearly define all outcomes, exposures, predictors, potential	P6-P7 Study
		confounders, and effect modifiers. Give diagnostic criteria, if	variables
		applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of	P5 Data source
measurement		methods of assessment (measurement). Describe comparability of	
		assessment methods if there is more than one group	
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	11	Explain how quantitative variables were handled in the analyses. If	P6-P7 Study
variables		applicable, describe which groupings were chosen and why	variables
Statistical methods	12	(a) Describe all statistical methods, including those used to control	P7-P8 Statistical
		for confounding	analysis
		(b) Describe any methods used to examine subgroups and	Not applicable
		interactions	1 tot approducto
		(c) Explain how missing data were addressed	P7 Study
		(*) 1	variables
		(d) If applicable, explain how loss to follow-up was addressed	P7 Study
		(a) 12 approacts, original new 1000 to 10110 if ap was auto-	variables
		(e) Describe any sensitivity analyses	Not applicable
D14		(<u>c</u>) 20041104 mily 041101111111 minispose	Trot approach
Results	12*	(a) Report numbers of individuals at each stage of study—eg	P8
Participants	13*		
		numbers potentially eligible, examined for eligibility, confirmed	Characteristics
		eligible, included in the study, completing follow-up, and analysed	of the study
		4) 6:	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,	P8
		clinical, social) and information on exposures and potential	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		(V_	
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	P11-12
		potential bias or imprecision. Discuss both direction and magnitude of any potential bias	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		4	
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.