Aetiological agents of adult community-acquired pneumonia in Japan: systematic review and meta-analysis of published data

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ABSTRACT

Objective Epidemiological information is essential in providing appropriate empiric antimicrobial therapy for pneumonia. This study aimed to clarify the epidemiology of community-acquired pneumonia (CAP) by conducting a systematic review of published studies in Japan.

Design Systematic review.

Data source PubMed and Ichushi web database (January 1970 to October 2022).

Eligibility criteria Clinical studies describing pathogenic micro-organisms in CAP written in English or Japanese, excluding studies on pneumonia other than adult CAP, investigations limited to specific pathogens and case reports.

Data extraction and synthesis Patient setting (inpatient vs outpatient), number of patients, concordance with the CAP guidelines, diagnostic criteria and methods for diagnosing pneumonia pathogens as well as the numbers of each isolate. A meta-analysis of various situations was performed to measure the frequency of each aetiological agent.

Results Fifty-six studies were included and 17 095 cases of CAP were identified. Pathogens were undetectable in 44.1% (95% CI 39.7% to 48.5%). Streptococcus pneumoniae was the most common cause of CAP requiring hospitalisation or outpatient care (20.0% (95% CI 17.2% to 22.8%)), followed by Haemophilus influenzae (10.8% (95% CI 7.3% to 14.3%)) and Mycoplasma pneumoniae (7.5% (95% CI 4.6% to 10.4%)). However, when limited to CAP requiring hospitalisation, Staphylococcus aureus was the third most common at 4.9% (95% CI 3.9% to 5.8%). Pseudomonas aeruginosa was more frequent in hospitalised cases, while atypical pathogens were less common. Methicillin-resistant S. aureus accounted for 40.7% (95% CI 29.0% to 52.4%) of S. aureus cases. In studies that used PCR testing for pan-respiratory viral pathogens, human enterovirus/human rhinovirus (9.4% (95% CI 0% to 20.5%)) and several other respiratory pathogenic viruses were detected. The epidemiology varied depending on the methodology and situation.

Conclusion The epidemiology of CAP varies depending on the situation, such as in the hospital versus outpatient setting. Viruses are more frequently detected by exhaustive genetic searches, resulting in a significant variation in epidemiology.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The epidemiology of community-acquired pneumonia varies among reports, and the proportion of cases due to Streptococcus pneumoniae and the frequency of atypical pathogens vary across countries. Although individual reports have been published, the situation of aetiological agents at the national level remains to be fully elucidated in Japan. In addition, understanding the national epidemiology of antibiotic resistance can help to promote antimicrobial stewardship and select empiric therapy, and vigorous testing for respiratory pathogen viruses may lead to significant differences in pathogen frequencies. We aimed to clarify these issues by conducting a meta-analysis.

WHAT THIS STUDY ADDS

⇒ The epidemiology of community-acquired pneumonia was found to vary widely depending on methodologies and the patient setting, such as inpatient versus outpatient care. Staphylococcus aureus and Pseudomonas aeruginosa were more common in hospitalised patients, and the frequency was even higher in elderly and critically ill patients. In addition, methicillin-resistant S. aureus was found in 40% of cases of community-acquired pneumonia.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Vigorous genetic testing significantly increases the detection of viruses, especially respiratory pathogens and the advent of COVID-19 is expected to further the understanding of epidemiological agents.

INTRODUCTION

Pneumonia, including aspiration pneumonia, remains a significant cause of death despite advances in medical care and antimicrobial agents. Inadequate empiric therapy increases the risk of death or treatment failure and is one factor that defines the prognosis of pneumonia. In addition,
unnecessary administration of broad-spectrum antimicrobial agents in the treatment of pneumonia should be avoided due to cost, adverse effects and antimicrobial selection pressure. Therefore, it is essential to surmise the causative micro-organisms and select an appropriate initial antimicrobial agent based on the background of pneumonia, such as the community, medical care or hospital setting, while conducting a microbiological search by sputum, blood culture and serological tests as necessary.

In addition, with medical advances and more patients receiving intensive medical care or antimicrobial agents, pneumonia should be treated with an awareness of antimicrobial resistance (AMR). Drug resistance, such as with methicillin-resistant *Staphylococcus aureus* (MRSA), cannot be ignored, not only in the hospital setting but also in the community. Even though broad-spectrum antimicrobial agents are widely used and the proportion of cases due to AMR is small, measures are still needed to recommend the prescribing of antimicrobial agents according to the AMR rate in the community, in order to further improve antimicrobial stewardship alongside global efforts against AMR. To this end, appropriate epidemiological data are required for each country or region, and more reliable and large-scale data are needed.

We conducted this systematic review of community-acquired pneumonia (CAP) in Japan to clarify the epidemiology of pathogenic micro-organisms and the frequency of drug resistance in CAP in Japan. In addition, because it is presumed that the epidemiology of CAP in a given area differs depending on the background and testing methods, we organised the data and performed a meta-analysis to clarify the epidemiology of pathogenic micro-organisms.

**MATERIAL AND METHODS**

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Meta-analysis of Observational Studies in Epidemiology statement.

**Search strategy and inclusion/exclusion criteria**

Three evaluators (YF, KS and TM) independently searched the PubMed and Ichushi web databases for articles published from January 1970 to October 2022 in English and Japanese, respectively. We collected articles dealing with CAP cases in Japan without limiting the pathogenic micro-organisms mentioned and regardless of the study type or endpoint. All studies that mentioned the aetiological organism and presented its data were included in the review. The search terms were “pneumonia” and its MeSH term, “community-acquired,” “Japan” and “Japanese” in PubMed, while the corresponding Japanese terms were used to search the Ichushi web database. Reports were required to be complete articles written in English or Japanese. Exclusion criteria were as follows: (1) studies involving children (<15 years old), (2) case reports or reviews, (3) pathogen-specific studies, (4) conference presentations, (5) studies involving only outpatients, (6) studies that did not exclude healthcare-associated pneumonia (HCAP) or nursing HCAP (NHCAP) as defined by the Japanese Respiratory Society (JRS) and (7) studies with duplicate eligible patients, such as studies with overlapping periods at the same medical institution. However, we could not exclude cases that may have been partially duplicated in multicentre studies. Studies conducted at a time before the official publication by the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) and the JRS of guidelines on HCAP and NHCAP may have included HCAP/NHCAP patients. Papers that included HCAP/NHCAP were excluded, but those that mentioned the exclusion of applicable patients, even if incomplete, were included. NHCAP is a modification of the HCAP concept suited to the Japanese healthcare system. Although the need to make a uniform distinction between HCAP/NHCAP in CAP is controversial, we chose to do so because many studies were conducted at a time when the HCAP/NHCAP distinction was widely accepted.

**Data collection**

We surveyed the eligible studies and extracted the following data: type and duration of the study, study site, patient setting (inpatient vs outpatient), number of patients in each study, inclusion criteria (age and severity), concordance with the ATS/IDSA guidelines on CAP or the JRS guidelines on CAP, diagnostic criteria, and methods for diagnosing pneumonia pathogens as well as the numbers of each isolate.

**Microbiological search**

When micro-organisms are isolated from patients with CAP, it is necessary to distinguish between pneumonia-causing and colonised micro-organisms. However, some of the collected articles did not clearly distinguish between pathogenic and detectable micro-organisms. For this reason, we also did not distinguish between them. However, the specific criteria for the microbiological search were extracted from the articles and summarised separately.

Gram stain and culture volume criteria were investigated for bacteria. Many articles did not adequately refer to the microscopic evaluation of sputum, but these were not excluded. Serological diagnostic criteria were investigated for atypical pathogens such as *Mycoplasma pneumoniae*. In addition, rapid diagnostics were extracted for *Streptococcus pneumoniae*, *Legionella pneumophila* and *M. pneumoniae*. For virus detection, serodiagnosis and rapid influenza diagnostics were used in some reports, while PCR was used for pan-respiratory pathogenic viruses in a few reports. Studies that used genome sequencing to analyse micro-organisms from the microbiome or 16S rRNA perspective were excluded from this review.
because they were too few to be integrated. In addition to MRSA, Pseudomonas aeruginosa and Enterobacteriales were also included as Gram-negative rods that can acquire AMR from the perspective of drug-resistant bacteria and were defined as potentially resistant Gram-negative bacilli (PRGNB).

Statistical analysis
Data were analysed using Review Manager V.5.4.1 (Cochrane Collaboration, London, UK). The random-effects model and generic inverse variance method were used to tabulate the data. Before the meta-analysis, SEs were calculated using the Agresti-Coull method, and meta-analyses were conducted for each target microorganism. Because several articles limited the target population to the elderly (generally 65 years and older) and severe CAP with mechanical ventilation, these were separately analysed as subgroups. I² statistics were used to assess the heterogeneity of the original papers.

Patient and public involvement
Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this study.

RESULTS
As shown in figure 1, a search was conducted based on the PRISMA recommendations, and 56 eligible papers were extracted during the study period. Forty-eight papers were in English and eight were in Japanese. The characteristics and details of the articles included are presented in table 1 and online supplemental table. A total of 17 095 CAP cases were identified, and the median number of eligible patients was 215 (range 18–1875). Eighteen studies (32.1%) were based on the 2007 ATS/IDSA guidelines for CAP. Twenty-two studies (39.3%) selected the target CAP according to the JRS guidelines or the original diagnostic criteria. However, the criteria in most studies were in accordance with ATS/IDSA, excluding immunodeficiency, malignancy and recent history of hospitalisation. Two studies (3.6%) excluded severe CAP, and another (1.8%) considered the possibility of mixing HCAP/NHCAP in the full review, although CAP was an inclusion criterion.

Fifty-two studies (92.9%) described criteria for determining the causative microorganism detected (online supplemental table). Bacterial culture tests were often based on bacterial abundance greater than $10^7$ colony-forming unit (CFU)/mL or $10^5$–$10^6$ CFU/mL with a reasonable Gram stain result, positive blood cultures (when extrapulmonary sites were not evident), and positive cultures from pleural fluid or transthoracic needle aspirate specimens. The PA, CF and ELISA methods were used for serological tests for atypical pathogens or some viruses. Some studies used not only individual sera but also paired sera for diagnosis. Only two studies (3.6%) used PCR to detect pan-respiratory pathogenic viruses. In total, 44.1% of all cases were of unknown aetiology with no detectable pathogen (95% CI 39.7 to 48.5; online supplemental figure).

Table 1 Characteristics of the 56 studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Studies, n</th>
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<tbody>
<tr>
<td>Inclusion criteria</td>
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<tr>
<td>Concordant with ATS/IDSA guideline</td>
<td>18</td>
</tr>
<tr>
<td>Original criteria (partial concordance with ATS/IDSA guidelines)</td>
<td>22</td>
</tr>
<tr>
<td>Not described</td>
<td>16</td>
</tr>
<tr>
<td>Patient limitation (including criteria)</td>
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<tr>
<td>Age (elderly patients)</td>
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<tr>
<td>Age and severity (elderly patients under mechanical ventilation)</td>
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<td>Study setting</td>
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<tr>
<td>Hospitalised</td>
<td>46</td>
</tr>
<tr>
<td>Description of diagnostic criteria for micro-organisms</td>
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<td>Atypical pathogen</td>
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<tr>
<td>Virus</td>
<td>17</td>
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<tr>
<td>Rapid diagnostics</td>
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<td>Retrospective</td>
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<td>Prospective</td>
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<tr>
<td>Publication period</td>
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<tr>
<td>1990–1999</td>
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</tr>
<tr>
<td>2000–2009</td>
<td>17</td>
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<tr>
<td>2010–2022</td>
<td>37</td>
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<tr>
<td>ATS/IDSA, American Thoracic Society/Infectious Diseases Society of America.</td>
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</table>
Epidemiology of CAP in inpatients and outpatients

Ten articles26 27 29 32 35–38 41 58 searched for pathogenic microorganisms in a total of 3155 patients with CAP, including outpatients. The results of the meta-analysis are shown in figure 2. *S. pneumoniae* was the most common pathogen (20.0% (95% CI 17.2% to 22.8%)), followed by *Haemophilus influenzae* (10.8% (95% CI 7.3% to 14.3%)), *M. pneumoniae* (7.5% (95% CI 4.6% to 10.4%)) and *C. pneumoniae* (3.3% (95% CI 1.1% to 5.5%)); less common were *Moraxella catarrhalis* (2.0% (95% CI 1.4% to 2.6%)), *S. aureus* (1.9% (95% CI 0.9% to 2.9%)) and influenza (0.7% (95% CI 0% to 1.6%)). In this category, only one study included the elderly, but did not provide sufficient data for an analysis of differences in microbial epidemiology in the elderly (online supplemental figure).

Epidemiology of patients with CAP requiring hospitalisation

Forty-six studies17–25 28 30 31 33 34 39 40 42–54 56 57 59–72 included a total of 13940 patients hospitalised with CAP. A meta-analysis of these studies is shown in figure 3. *S. pneumoniae* was the most common pathogen (16.2% (95% CI 14.1% to 18.2%)), followed by *H. influenzae* (6.9% (95% CI 6.0% to 7.9%)) and *S. aureus* (4.9% (95% CI 3.9% to 5.8%)); *M. pneumoniae* and *C. pneumoniae*, which were more frequent in the outpatient setting, were less common. In contrast, *P. aeruginosa* was more common than in the outpatient-included setting.

In a separate meta-analysis of six studies of elderly patients and two studies of elderly patients on mechanical ventilation, *S. pneumoniae*, *H. influenzae*, *M. pneumoniae* and *C. pneumoniae* were less common and *S. aureus* and *P. aeruginosa* were more common among the elderly (online supplemental figure).

Epidemiology of using PCR to search for pathogenic microorganisms

A meta-analysis of two studies involving 207 cases58 66 in which PCR was performed in addition to traditional culture and serological searches for pathogenic microorganisms is shown in figure 4. *S. pneumoniae* was the most common pathogen (23.1% (95% CI 13.1% to 33.1%)), followed by *H. influenzae* (11.4% (95% CI 0% to 24.5%)), human enterovirus/human rhinovirus (9.4% (95% CI 0% to 20.5%)), human metapneumovirus (4.6% (95% CI 1.6% to 7.6%)), respiratory syncytial virus (4.2% (95% CI 1.2% to 7.1%)) and several other viruses. These results differed significantly from the epidemiology when PCR was not used (online supplemental figure).

Drug resistance and chronological trend

PRGNB accounted for 7.1% (95% CI 5.9% to 8.3%) of all cases. When only articles that described MRSA and/or methicillin-susceptible *S. aureus* separately were selected, MRSA was accounted for 40.7% of cases (95% CI 29.0% to 52.4%) in 30 studies,17 30 31 33 34 39 40 42 44–47 51 52 54 55 57 60–63 65–68 70 72 with *S. aureus* as the causative pathogen in 427 cases (online supplemental figure).

In addition, to focus on the study period, 8 studies17–22 25 29 up to the year 2000 and 13 studies24 52 53 60 62–64 66–72 after 2010 were selected to compare the frequency of detection of *S. pneumoniae* and PRGNB. Although there was no change in *S. pneumoniae*, the frequency of PRGNB isolation increased from 6.3% (95% CI 2.9% to 9.7%) to
the epidemiology of CAP was based on the exclusion of patients with recent antimicrobial exposure and hospitalisation as much as possible, the underlying diseases and the antimicrobial therapy they received might have influenced the epidemiology, especially in elderly patients. Furthermore, because *S. aureus* tends to cause severe pneumonia and atypical pneumonia is less likely to result in hospitalisation, differences in the frequency of isolation can likely be seen when limited to CAP that requires hospitalisation.

In our meta-analysis, *S. pneumoniae* was the most common isolate, accounting for around 20% of CAP cases. Although the frequency of *S. pneumoniae* is known to vary by region worldwide, from about 30% in Europe to 15% in the USA, it has always been the most isolated common bacteria. The regional differences may be due in part to vaccination. In Japan, the estimated vaccination coverage of the 23-valent pneumococcal polysaccharide vaccine among those aged 65 years and older was 26.8% in 2008. However, a subsequent campaign led to an estimated cumulative vaccination coverage of 74% in 2018, suggesting that vaccination is widely accepted. However, the meta-analysis showed that the actual isolation frequency during this period was about the same. It may be some time before we can discuss the impact of the vaccine on pneumococcal pneumonia prevalence, as it became a routine national immunisation programme in 2014, and annual vaccination rates have increased since then. Only a few papers mentioned AMR in *S. pneumoniae*, so trends in drug resistance could not be explored further.

*S. aureus* was isolated more frequently, especially in CAP requiring hospitalisation. MRSA was found in about 40% of such cases, which is an important finding, especially in severe cases of CAP. It remains an open question whether anti-MRSA therapy should be empirically added. Although a separate Japanese respiratory pathogen surveillance covered all lower respiratory tract infections, the MRSA rate for all *S. aureus* infections was still 48.3%, so MRSA in Japan cannot be ignored. The genotype of MRSA was not explored in this review.

In addition, only some specific references to AMR could be made in this systematic review and suggested that the frequency of PRGNB isolation is on the rise. However, trends in AMR could not be explored. Although rare as a causative micro-organism for CAP, the need to increase awareness of AMR in empirical therapy is nevertheless suggested, and future work should investigate trends in AMR.

Influenza affects an estimated 10 million people in Japan yearly, but influenza viruses have been detected in small numbers among adult CAP. Influenza vaccination coverage among persons aged 65 years and older has remained constant at around 40%–55% for the past 20 years. Furthermore, the use of anti-influenza drugs is widely recommended in Japan, which is presumed to have some effect on suppressing pneumonia. However, since rapid diagnostics are commonly used,

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**Figure 5** Change in frequency of *Streptococcus pneumoniae* and PRGNB over time. PRGNB, potentially resistant Gram-negative bacilli.

10.5% (95% CI 6.5% to 14.4%) (figure 5, online supplemental figure).

**DISCUSSION**

In this systematic review and meta-analysis, we collected all articles describing the epidemiology of CAP in Japan that were available in public databases and investigated the aetiological micro-organisms. The results showed that (1) *S. pneumoniae* was the most common pathogen (around 20%), although a wide range of atypical pathogens was also seen; (2) *S. aureus* was more frequently isolated in CAP requiring hospitalisation; (3) *S. aureus* and *P. aeruginosa* were more frequently isolated in elderly patients; (4) isolation of viruses is also common in CAP and an exhaustive examination for viruses can significantly change the epidemiology of the disease; (5) the isolation rates of MRSA and PRGNB observed in CAP mean that treatment should be considered while being cognizant of AMR and (6) although no difference was observed between the isolation frequency of *S. pneumoniae* before 2000 and after 2010, the isolation frequency of PRGNB was found to be on the rise.

CAP is one of the most commonly encountered infectious diseases in clinical practice, and the causative microbial epidemiology has been widely reported. However, as reported in other countries, even with aggressive traditional testing, the causative micro-organism could not be identified in about half of the cases reported in Japan. When the frequency of isolation was examined, the epidemiology varied between studies that included both inpatients and outpatients and those that were limited to inpatients. Specifically, the isolation frequency of atypical pathogens decreased, whereas that of *S. aureus* and *P. aeruginosa* increased in CAP requiring hospitalisation, consistent with reports from other countries. The higher isolation frequency in CAP requiring hospitalisation among elderly and critically ill patients contributed to the change in epidemiology. Although...
the prevalence may be underestimated in terms of sensitivity.

Recent advances in viral testing methods have changed our understanding of pneumonia epidemiology.6–8,41–46 Although this study could not be fully validated due to the paucity of available references, it was confirmed that respiratory pathogen viruses are frequently detected in cases of CAP in Japan, as in other countries. While testing methods for determining that a virus is the definitive cause of CAP have not been fully established, and the pathogenicity of the detected viruses needs to be discussed separately,7 the epidemiology of pneumonia in terms of pathogen isolation is expected to change substantially in the future because genomic testing panels that can detect pan-respiratory pathogen viruses67 are being applied in respiratory tract infections in the COVID-19 era. Further high-quality surveillance of domestic adult CAP is expected through genomic testing. Furthermore, with the growing understanding of the microbiome, the concept of pneumonia and pathogen epidemiology is on the verge of change.68 69 Of course, not only advances in detection methods but also in the frequency of pathogens can change over time due to drug resistance and vaccines.

The limitations of this review and meta-analysis are as follows. (1) The quality of the articles and the detection techniques varied, so the frequency of atypical pathogens and viruses may not have been accurately reflected. This problem was resolved by conducting a separate analysis of viruses because the addition of an exhaustive PCR-based search for viruses was shown to significantly impact the epidemiological results. (2) When a multicentre study was included, case overlap with other published studies was possible. Although we eliminated duplications as much as possible in the full review, a certain degree of duplication cannot be ruled out. (3) HCAP/NHCAP cases were not adequately excluded, especially in articles published before the early 2000s. There is some debate as to whether it is necessary to distinguish between HCAP and NHCAP, and the primary direction has been to assess the risk of AMR according to individual risk factors; however, we chose to distinguish HCAP/NHCAP in this study on the basis that many included studies were conducted at a time when the HCAP/NHCAP distinction was widely accepted. In this systematic review, we would have used the intended HCAP/NHCAP exclusion criteria if they had been in place. (4) Some studies excluded severe CAP, but because the definition of severe CAP was not uniform across studies, it was not included in the exclusion criteria in this systematic review. (5) Many papers lacked sufficient precision about the distinction between carriers and causative organisms. For viruses in particular, a method for clearly distinguishing between them needs to be properly established. Regardless, the pathogenicity of the micro-organisms detected is controversial60 and was not considered in this study.

CONCLUSIONS

In conclusion, we conducted a systematic review of the epidemiology of CAP in Japan by comprehensively collecting all published articles on the isolation of pathogenic micro-organisms and conducting an epidemiological survey. With the further advancement and dissemination of testing technology and the spread of COVID-19, the epidemiology of CAP may change and warrant further investigation.

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