Original Article

High Incidence of Community-Acquired Pneumonia among Rapidly Aging Population in Japan: A Prospective Hospital-Based Surveillance

Masahiro Takaki[1†], Takahiro Nakama[2†], Masayuki Ishida[1†], Hitomi Morimoto[3], Yuka Nagasaki[3], Rina Shiramizu[1], Naohisa Hamashige[4], Masayuki Chikamori[5], Laymyint Yoshida[1], Koya Ariyoshi[1], Motoi Suzuki[1], and Konosuke Morimoto[1]*

[1]Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University, Nagasaki 852-8523; and [2]Department of Respiratory Medicine, [3]Department of Laboratory, [4]Department of Internal Medicine, and [5]Department of Dialysis, Chikamori Hospital, Kochi 780-0052, Japan

SUMMARY: The age-group-specific incidence and etiological patterns of community-acquired pneumonia (CAP) have not been fully established in Japan. A 2-year prospective surveillance was conducted in Kochi city, Western Japan. All CAP patients aged ≥15 years who visited a community-based hospital were enrolled in the study. Clinical samples were examined by conventional bacterial culture and urinary antigen tests, and 6 bacterial pathogens and 16 respiratory viruses were identified from sputum samples by multiplex polymerase chain reaction assays. The age-group-specific incidence of CAP was estimated using a population-based data set of the total number of outpatients in the whole city. Ninety of the 131 enrolled patients, 68.7% were positive for respiratory pathogens. *Streptococcus pneumoniae* was the leading bacterial pathogen identified (28.2%). Respiratory viruses were identified in 36 patients (27.5%), and human entero–rhinovirus was the most common (13.3%) among them. The estimated overall incidence of adult CAP in Kochi was 9.6 per 1,000 person-years (PY); the estimated age group-specific incidence was 3.4, 10.7, and 42.9 per 1,000 PY for those aged 15–64, 65–74, and ≥75 years, respectively. The high incidence of CAP in these rural city of Japan, probably reflects the substantial aged population. *S. pneumoniae* and respiratory viruses play important roles in CAP in all age groups.

INTRODUCTION

Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality among adults worldwide (1). According to recent estimates, lower respiratory tract infections, including CAP, are the fourth largest cause of death, and 1.9 million adults aged ≥15 years die every year from lower respiratory tract infections (2).

Elucidating the true burden and etiological patterns of CAP among the adult population is crucial for making a rational public health policy; however, there is a lack of such information in most countries. Limited reports have indicated that CAP epidemiology varies between countries. The annual incidence of adult CAP was 2.8 per 1,000 person-years (PY) in North America (3), 1.2 per 1,000 PY in Spain (4), 3.7–10 per 1,000 PY in Germany (5), and 5.8 per 1,000 PY in Thailand (6). Although *Streptococcus pneumoniae* is the leading bacterial cause of CAP regardless of geographical area (7), the secondary causative pathogen differs across settings (1). Studies have shown that respiratory viruses, including influenza virus, rhinovirus, and coronavirus, play putative causative roles in the development of adult CAP (8), and the prevalence of these viral pathogens varies between seasons (9). However, the impact of circulating respiratory viruses on the adult CAP burden has been rarely investigated, and the regional differences remain largely unknown.

Aging of the population is another major determinant of CAP epidemiology. The incidence of adult CAP increases with age and is the highest among elderly people (3,4,6,7); the case fatality rate of CAP is particularly high in this age group (3,10). It is plausible that the pathophysiological mechanism and etiological patterns of CAP in elderly people may differ from those in younger age groups. However, it is challenging to provide age-stratified incidence data on CAP. Only few studies have investigated bacterial and viral pathogens in the context of CAP incidence separately in the older and younger populations. Moreover, reliable incidence estimates of adult CAP are not available from Asian countries, including Japan, which has the world's fastest aging population (11).

The present prospective hospital-based survey was therefore conducted in Kochi city, a typical rural city

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*Corresponding author: Mailing address: Department of Clinical Medicine Institute of Tropical Medicine, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan. Tel: +81-95-819-7842, Fax: +81-95-819-7843, E-mail: komorimo@nagasaki-u.ac.jp
†These authors contributed equally to this work.

with a rapidly aging population in Western Japan; a novel approach outside the setting of a population-based study was adopted for estimating the overall and age-group-specific incidence rates of adult CAP in the Japanese population and for establishing a comprehensive etiology of adult CAP.

MATERIALS AND METHODS

Study setting: A prospective hospital-based surveillance was conducted in Kochi city, Western Japan. According to the National Population Census Survey, the total population of the city in April 2009 was 340,208, with 63.7%, 11.2%, and 11.4% of the population belonging to the age groups 15–64, 65–74, and ≥ 75 years, respectively. Sixty non-psychiatric hospitals with 8,332 beds were present in the city. At the time of the study, the National Program for administration of the 23-valent pneumococcal polysaccharide-vaccine (PPV23) had not been implemented in Japan.

Chikamori Hospital, a representative community-based private hospital located in Kochi city, has 338 beds for non-psychiatric patients, and it provides primary, secondary, and tertiary care for residents. This hospital accounts for 5.6% of the total number of non-psychiatric outpatients across all hospitals in the city. The implementation of universal health insurance in Japan has resulted in 70% and 80–90% coverage of the medical costs for people aged < 70 and ≥ 70 years, respectively, regardless of being in the private or public sector (12). Therefore, the characteristics of patients visiting this hospital are not expected to be significantly different from those of patients visiting public hospitals.

Enrollment criteria: During the study period from May 2008 to April 2010, all outpatients were screened by hospital physicians, and eligible CAP patients were identified on the basis of a standardized case definition established from the British Thoracic Society guidelines (1). All patients aged ≥ 15 years who visited the study hospital with any respiratory symptoms compatible with pneumonia and showed consolidation on chest X-ray (CXR) were included in the present study. Two pulmonologists and an experienced physician interpreted all CXRs independently; a case was categorized as pneumonia if at least 2 of the 3 examining physicians agreed on the presence of consolidation.

Healthcare-associated pneumonia (HCAP) and hospital-acquired pneumonia (HAP) were diagnosed according to the guidelines established by the American Thoracic Society and Infectious Diseases Society of America (13); cases presenting with HCAP or HAP were excluded from the present study.

Demographic and clinical information was collected from patients and medical charts using a standardized data collection form. Informed consent was obtained from all the participants, following which sputum samples were collected; if required, sputum was induced by inhalation of hypertonic saline solution. CXRs were obtained from all patients within 24 h of admission. Disease severity was assessed using the A-DROP score (14), which is a modified version of the CURB-65 score and uses 5 clinical features: patient age (male ≥ 70 years, female ≥ 75 years), urea of ≥ 21 mg/dl and/or dehydra-

tion, SpO2 of ≤ 90% and/or PaO2 ≤ 60 torr, confusion, and systolic blood pressure of ≤ 90 mmHg.

Laboratory testing: Clinical specimens were immediately transported to the hospital laboratory. Gram staining was performed on each sputum specimen, and specimen quality was evaluated according to Miller and Jones' Classification by trained laboratory technicians (15). The number of colony-forming units per milliliter (cfu/ml) was assessed using a conventional quantitative culture (16). The samples were considered to be positive upon isolation of the common bacterial pathogens, namely *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*, from the sample. The samples were also considered positive if uncommon, non-normal bacterial flora were identified at counts of $\geq 1 \times 10^6$ cfu/ml from good-quality samples (i.e., Miller and Jones' Classification of P2 or P3) and consistent findings were obtained upon Gram staining (17).

Sputum samples were further tested by polymerase chain reaction (PCR) assays for identifying bacterial and viral pathogens. The presence of 3 typical (*S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*) and 3 atypical (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila*) bacteria was tested by multiplex-PCR in the hospital laboratory, as described previously (18). Sixteen respiratory viruses (*influenza A virus H1/H3* [FLUA], *influenza B virus* [FLUB], *respiratory syncytial virus* [RSV], *human adenovirus* [HAdV], *human enterovirus* [HEV] or *human rhinovirus* [HRV], *human bocavirus* [HBoV], *human metapneumovirus* [HMPV], *human parainfluenza viruses* [HPIV] types 1–4, and *human coronavirus OC43* [HCoV-Oc43], *HCoV-229E*, *HCoV-NL63*, and *HCoV-KU1*) were identified using the xTAG RVP FAST assay (Abbott Laboratories, North Chicago, IL, USA) and Luminex system (Luminex Corporation, Austin, TX, USA) according to the manufacturer's protocol. Broadly reactive primers that amplified RNA from either HRVs or HEVs were used in this study, and the results were reported as entero–rhinovirus (HEV/HRV). A urinary antigen test for *S. pneumoniae* and *L. pneumophila* was also performed using commercial kits (Binax NOW *Streptococcus pneumoniae*, Binax NOW *Legionella*; Alere Inc., Waltham, MA, USA).

Data analyses: Data were analyzed using STATA Version 11.2 (STATA Corp., College Station, TX, USA). Patient' characteristics were compared by age group using χ^2 or Fisher's exact tests for categorical variables and t tests for numerical variables, and 95% confidence intervals (CIs) were calculated assuming a Poisson distribution.

Estimation of age-group specific incidence rates: To estimate the overall and age-group-specific incidence rates of CAP in Kochi city, a previously employed method (5,19) was modified as follows. Patient were categorized into the age groups 15–64 (younger adult), 65–74 (early elderly), and ≥ 75 (late elderly) years. The hospital database consisting of the International Classification of Diseases, 10th revision (ICD-10) coding was screened, to identify potentially eligible pneumonia patients with codes J10–J18 and J69, and their medical records and CXRs were reviewed; this was done to ensure that all eligible cases were enrolled. The ratio of the

number of CAP patients to the total number of outpatients in Chikamori Hospital was then determined. Following this, the annual number of CAP patients in the whole city was estimated by multiplying the total number of non-psychiatric outpatients across all hospitals in the city by the CAP/outpatient ratio of Chikamori Hospital on the basis of the assumption that this ratio did not differ with variations in clinical setting in Kochi city. The total number of non-psychiatric outpatients in the city from January 2008 to December 2009 was obtained from Japan's Ministry of Health, Labour and Welfare database. Following this, age-group-specific incidence rates were calculated by dividing the estimated annual number of CAP patients of a certain age group by the corresponding population (of the same age group) in the city; the latter was estimated from the National Census Survey.

Ethics statement: The study was approved by the Institutional Review Board (IRB) of Chikamori Hospital, Kochi, and the IRB of the Institute of Tropical Medicine at Nagasaki University. Informed consent was obtained in writing from all the participants or their guardians prior to enrolment.

RESULTS

Demographic data and clinical presentation: A total of 131 patients, including 68 and 63 patients in the 2008/2009 and 2009/2010 seasons, respectively, were prospectively enrolled in the study. Both seasons showed a similar distribution of cases with a peak in January. The demographic and clinical characteristics of the patients are shown in Table 1. Almost 70% of the patients were male, and the median age was 77 years (interquartile range: 63–84 years); 73% and 60% of the study participants were elderly patients aged ≥ 65 and ≥ 75 years, respectively. The majority of the participants were hospitalized, and the overall mortality rate was 4.6% (95% CI: 1.7%–10.0%). Antibiotics had been prescribed for 41 patients (35%) prior to their

Table 1. Demographic and clinical characteristics of 131 study patients

Characteristics	Total	Age group (y)		
		15–64	65–74	≥ 75
Patients (%)	131	35 (26.7)	19 (14.5)	77 (58.8)
Age (y), median (IQR)	77 (63–84)	54 (39–59)	71 (69–73)	83 (79–87)
Sex	131	35	19	77
Male (%)	89 (67.9)	22 (62.9)	13 (68.4)	54 (70.1)
Female (%)	42 (32.1)	13 (37.1)	6 (31.9)	23 (29.9)
Smoking status	113	31	14	68
Never smoker (%)	53 (46.9)	15 (48.4)	7 (50.0)	31 (45.6)
Current smoker (%)	11 (9.7)	6 (19.4)	0	5 (7.4)
Ex-smoker (%)	49 (43.4)	10 (32.3)	7 (50.0)	32 (47.1)
Comorbidity	130	35	19	76
Any diseases (%)	96 (73.8)	18 (51.4)	12 (63.2)	67 (88.2)
Chronic heart failure/ischemic heart disease (%)	50 (38.5)	5 (14.3)	5 (26.3)	32 (42.1)
Chronic respiratory disorder (%)	40 (30.8)	9 (25.7)	0	31 (40.8)
Cerebrovascular disorder (%)	32 (24.6)	0	7 (36.8)	25 (32.9)
Others[1] (%)	58 (44.6)	9 (25.7)	7 (36.8)	42 (55.3)
None (%)	34 (26.2)	17 (48.6)	7 (36.8)	9 (11.8)
Symptoms and signs	130	35	19	76
Cough (%)	77 (59.2)	25 (71.4)	13 (68.4)	39 (51.3)
Fever (%)	52 (40.0)	20 (57.1)	6 (31.6)	26 (34.2)
Dyspnea (%)	44 (28.7)	14 (16.7)	5 (26.3)	25 (32.9)
Treatment setting	131	35	19	77
Hospital treatment (%)	125 (95.4)	32 (91.4)	19 (100)	74 (96.1)
Preceding antibiotic data	117	30	17	70
Preceding antibiotics use (%)	41 (35.0)	11 (36.7)	5 (29.4)	25 (35.7)
A-DROP (%)	123	32	18	73
Mild (0)	22 (17.9)	18 (56.3)	4 (22.2)	0
Moderate (1–2)	74 (60.2)	14 (43.8)	10 (55.6)	50 (68.5)
Severe (3)	17 (13.8)	0	3 (16.7)	14 (19.2)
Very Severe (4–5)	10 (8.1)	0	1 (5.6)	9 (12.3)
Ventilator support	131	35	19	77
Invasive ventilation (%)	6 (4.6)	1 (2.9)	1 (5.3)	4 (5.2)
Noninvasive ventilation (%)	4 (3.1)	1 (2.9)	1 (5.3)	2 (2.6)
Outcome	131	35	19	77
Living (%)	125 (95.4)	36 (100)	17 (89.5)	73 (94.8)
Deceased (%)	6 (4.6)	0	2 (10.5)	4 (5.2)

IQR: interquartile range, 25–75%.
[1]: Others included diabetes mellitus ($n = 20$, 15.4%), liver dysfunction ($n = 19$, 14.6%), malignancies ($n = 19$, 14.6%), chronic kidney disease ($n = 14$, 10.8%) and autoimmune disorders ($n = 6$, 4.6%).

hospital visit. Compared with the younger adult patients (15–64 years), the frequency of severe (A-DROP score of 3) and very severe (A-DROP scores of 4 and 5) disease was higher among the early elderly (65–74 years) and late elderly (≥75 years) patients ($p < 0.013$ and $p < 0.001$, respectively). The frequency of comorbidities was also higher among late elderly patients than among younger adult and early elderly patients ($p < 0.001$ and $p < 0.009$, respectively); the prevalence of chronic heart disease was particularly high among the elderly patients. The late elderly patients, however, were less likely to present with cough than the younger adult patients ($p = 0.046$). Other characteristics were almost identical between the different age groups.

Detection of respiratory pathogens: Sputum samples obtained from 131 patients were tested by conventional culture and multiplex-PCR, while urinary antigen tests for *S. pneumoniae* and *L. pneumophila* were performed on 126 and 123 patients, respectively.

Of the 131 samples tested by conventional culture, at least 1 pathogenic bacterium was isolated from 41 (31.3%) samples. Multiplex-PCR revealed that, 61 (44.6%) samples were positive for DNA from at least 1 bacterium, including 4 dual-positives (*S. pneumoniae + H. influenzae*, $n = 3$; *H. influenzae + M. catarrhalis*, $n = 1$). On combining all results, 90 (68.7%) cases were found to be positive for at least 1 of the respiratory pathogens. *S. pneumoniae* was the most common bacterial pathogen (28.2%) identified in all the age groups, followed by *H. influenzae* (18.3%), *M. catarrhalis* (6.1%), and *M. pneumoniae* (5.3%) (Table 2). *H. influenza* was more prevalent among late elderly patients than among younger adult patients ($p = 0.07$). In contrast, the detection rate of *M. pneumoniae* was the highest among the younger adult patients.

All samples were tested for the presence of viruses, and 36 (27.5%) samples were found to be positive for at least 1 respiratory virus, including 2 dual-positives (HEV/HRV + HAdV, $n = 1$; RSV + HAdV, $n = 1$) (Table 3). HEV/HRV was the most common virus identified, followed by RSV. Thirteen of the 36 virus-positive samples were negative for bacteria, and RSV was the most common virus ($n = 5$, 38.5%) in these samples. Viral–bacterial co-detection was observed in 23 of the 36 (63.9%) virus-positive samples; 16 of 20 (80.0%) HEV/HRV-positive samples and 2 of 7 (28.6%) RSV-positive samples were also positive for bacteria. Intriguingly, patients infected with *S. pneumoniae* were more likely to have a co-infection with respiratory viruses than other patients (50% vs 15%, $p = 0.002$), independently of the age group.

Incidence of CAP: According to the hospital ICD-10 database, 1,210 patients aged ≥15 years were registered in Chikamori Hospital with pneumonia (J10–J18 and J69) during the study period. Reviewing of medical records and CXRs resulted in the retrospective identification of an additional 185 CAP cases that were overlooked during the prospective screening. Thus, the enrollment rate of the prospective survey was 0.41 ($n = 131/316$). There were 249,609 outpatients in Chikamori Hospital during study period; the CAP/outpatient ratio of the hospital was therefore 0.127 (95% CI: 0.113–0.141). The total number of non-psychiatric outpatients across all hospitals in Kochi city from January 2008 to December 2009 was 4,687,300. Therefore, the annual number of adult CAP patients in the city was estimated to be 2,805 (95%CI: 2,504–3,132). The population of the city in April 2009 was 293,650 the overall incidence rate of adult CAP in Kochi was therefore estimated to be 9.6 (95% CI: 8.53–10.67) per 1,000 PY (Table 4). The age-group-specific incidence rate was the lowest in the group aged 15–64 years (3.4 per 1,000 PY) and approximately 12 times higher in the group aged ≥75 years (42.9 per 1,000 PY). The incidence of CAP associated with *S. pneumoniae* and respiratory viruses was also much higher in the older age group.

Table 2. Bacterial pathogens

	All age ($n = 131$)				15–64 y ($n = 35$)	65–74 y ($n = 19$)	≥75 y ($n = 77$)
	Culture (%)	PCR (%)	UATs[1] (%)	Total (%)	Total (%)	Total (%)	Total (%)
Bacteria[2]	41 (31.3)	61 (46.6)		76 (58.0)	20 (57.1)	13 (68.4)	43 (55.8)
S. pneumoniae[3]	14 (10.7)	27 (20.6)	24 (19.0)	37 (28.2)	10 (28.6)	9 (47.4)	18 (23.4)
H. influenzae	13 (9.9)	22 (16.8)	N.A.	24 (18.3)	3 (8.6)	2 (10.5)	19 (24.7)
M. catarrhalis	6 (4.6)	7 (5.3)	N.A.	8 (6.1)	2 (5.7)	1 (5.3)	5 (6.5)
M. pneumoniae	N.A.	7 (5.3)	N.A.	7 (5.3)	4 (11.4)	0	3 (3.9)
C. pneumoniae	N.A.	1 (0.8)	N.A.	1 (0.8)	1 (2.9)	0	0
L. pneumophila	N.A.	1 (0.8)	2 (1.6)	2 (1.5)	0	0	2 (2.6)
Haemophilus parainfluenzae	3 (2.3)	N.A.	N.A.	3 (2.3)	0	0	3 (3.9)
K. pneumoniae	3 (2.3)	N.A.	N.A.	3 (2.3)	0	0	3 (3.9)
S. aureus	3 (2.3)	N.A.	N.A.	3 (2.3)	0	1 (5.3)	2 (2.6)
E. coli	1 (0.8)	N.A.	N.A.	1 (0.8)	1 (2.9)	0	0
Klebsiella ozaenae	1 (0.8)	N.A.	N.A.	1 (0.8)	0	0	1 (1.3)

N.A.: not available.

[1]: Urinary antigen tests for *S. pneumoniae* ($n = 126$) and *L. pneumophila* ($n = 123$).

[2]: Two culture-positive bacteria in three samples (*S. pneumoniae + H. influenzae*, $n = 2$; *S. aureus + K. pneumoniae*, $n = 1$) and 2 PCR-positive bacteria in 4 samples (*S. pneumoniae + H. influenzae*, $n = 3$; *H. influenzae + M. catarrhalis*, $n = 1$). Altogether, there were 11 patients with 2 or 3 bacterial pathogens (*S. pneumoniae + H. influenzae*, $n = 6$; *H. influenzae + H. parainfluenzae*, $n = 2$; *S. pneumoniae + M. catarrhalis*, $n = 1$; *S. pneumoniae + H. influenzae + H. parainfluenzae*, $n = 1$; *S. pneumoniae + K. pneumoniae + S. aureus*, $n = 1$).

[3]: Including one blood culture result.

Table 3. Viral pathogens and co-detection with bacterial pathogens

	All age (n = 131)	15–64 y (n = 35)	65–74 y (n = 19)	≥ 75 y (n = 77)
Virus	36 (27.5)[1]	8 (22.9)	8 (42.1)	20 (26.0)[1]
HEV/HRV	20 (13.3)	4 (11.4)	4 (21.1)	12 (15.6)
RSV	7 (5.3)	2 (5.7)	1 (5.3)	4 (5.2)
HMPV	5 (3.8)	1 (2.9)	3 (15.8)	1 (1.3)
HAdV	2 (1.5)			2 (2.6)
FLUA	1 (0.8)			1 (1.3)
FLUB	1 (0.8)			1 (1.3)
HPIV	2 (1.5)	1 (2.9)		1 (1.3)
Combination	23 (17.6)	4 (11.4)	7 (36.8)	12 (15.6)
S. pneumoniae + HEV/HRV	9 (6.9)	1 (2.9)	3 (15.8)	5 (6.5)
+ RSV	1 (0.8)		1 (5.3)	
+ HMPV	3 (2.3)	1 (2.9)	2 (10.5)	
+ FLUB	1 (0.8)			1 (1.3)
H. influenzae + HEV/HRV	3 (2.3)	1 (2.9)	1 (5.3)	1 (1.3)
+ RSV	1 (0.8)			1 (1.3)
+ HPIV	1 (0.8)	1 (2.9)		
K. pneumoniae + HEV/HRV	1 (0.8)			1 (1.3)
S. pneumoniae + H. influenzae + HEV/HRV	1 (0.8)			1 (1.3)
S. pneumoniae + M. catarrhalis + HEV/HRV	1 (0.8)			1 (1.3)
S. pneumoniae + H. influenzae + HEV/HRV + HAdV	1 (0.8)			1 (1.3)

HEV/HRV: *human enterovirus* or *human rhinovirus*, RSV: *respiratory syncytial virus*, HMPV: *human metapneumovirus*, HAdV: *human adenovirus*, FLUA: *influenza A virus H1/H3*, FLUB: *influenza B virus*, HPIV: *human parainfluenza virus* types 1–4.
[1]: Including 2 dual detections (HEV/HRV + HAdV, n = 1; RSV + HAdV, n = 1).

Table 4. Age- and pathogen-specific CAP incidence in Kochi city (1,000 PY)

	Incidence (95% CI)			
	Total	All bacteria	S. pneumoniae	All viruses
All ages	9.55 (8.53–10.67)	5.54 (4.95–6.19)	2.70 (2.41–3.01)	2.62 (2.34–2.93)
15–64	3.40 (2.71–4.21)	1.94 (1.55–2.41)	0.97 (0.77–1.20)	0.78 (0.62–0.96)
65–74	10.72 (7.85–14.30)	7.33 (5.37–9.78)	5.08 (3.72–6.77)	4.51 (3.30–6.02)
≥ 75	42.85 (36.93–49.45)	23.93 (20.62–27.62)	10.01 (8.63–11.56)	11.13 (9.59–12.84)

DISCUSSION

The present study is the first to systematically investigate age-stratified incidence of adult CAP in the aging population of Japan. A high incidence of CAP was observed; *S. pneumoniae* was the most frequent bacterial pathogen to be identified regardless of the age group, while respiratory viruses were identified in 27.5% of the CAP cases. The incidence of CAP was particularly high in late elderly people aged ≥ 75 years.

Importantly, the present study revealed that *S. pneumoniae* was the most frequently detected bacterial pathogen, present in 28.2% of the participants of all age groups. However, the bacterial culture method yielded a lower positive rate of *S. pneumoniae* infection (10.7%); the higher rate of detection using the PCR technique is attributable to the lower sensitivity of conventional culture, particularly with patients who were pre-exposed to antibiotics. The detection of bacterial DNA by PCR has overwhelming advantages in pneumonia surveys, particularly in study settings where many patients have already received antibiotics (20).

The positive rate of *H. influenzae* detection was higher among the older patients, probably reflecting impaired mucociliary clearance and underlying chronic respiratory illness among them (21,22). *H. influenzae* is commonly involved in acute exacerbation of chronic bronchitis and chronic obstructive pulmonary disease (23). In fact, the present study revealed that such chronic respiratory diseases were more common among elderly people and were associated with *H. influenzae* but not *S. pneumoniae* positivity (results not shown). Enteric Gram-negative bacilli, including *Klebsiella* spp. and *Staphylococcus aureus*, were identified only from patients aged ≥ 75 years. The prevalence of comorbidity, particularly cerebrovascular disorders, is high among older people, and they are therefore at higher risk of aspiration pneumonia (24).

Respiratory viruses were associated with 27.5% of the CAP cases in the present study. A review of studies on viral pneumonia, which utilized PCR for testing the presence of respiratory viruses, reported viral detection in 22% of adult CAP cases (8), which is comparable with the findings of the present study. The virus HEV/HRV was identified with the highest frequency in the present study. Although HRV was not distinguished from HEV, the causative pathogen is more likely to be HRV because it is generally recognized as the most

frequent cause of upper respiratory tract infections.

The co-detection of viruses and bacteria particularly respiratory virus and *S. pneumoniae*, in the present study is consistent with other reports (8). Whether HRV is a bystander or plays an active role in the development of pneumonia remains unknown. In this context, infection with HRV, the most frequency identified viral pathogen in the present study, has been hypothesized to stimulate the adhesion of *S. pneumoniae* to airway epithelial cells via increased platelet-activating factor receptors (25). Moreover, Choi et al. have shown that HRV is frequently detected as a single pathogen from bronchoalveolar lavage fluid in patients with severe pneumonia (26). Taken together, these results indicate that HRV plays a role in predisposition to and the development of pneumonia. However, the present study does not provide a causal explanation for the observed phenomenon, owing to limited biological data. Further investigations are therefore required for clarifying the same.

Previous epidemiological studies failed to implicate causative pathogen in the majority (39% to 49.3%) of CAP cases (4,22), which could be explained by 2 factors. First, the sensitivity of conventional bacterial culture is decreased after antibiotic treatment. The count of bacterial pathogens is likely to be particularly low in hospital-based studies conducted in resource-rich settings where pre-hospital antibiotics are widely used. Second, a substantial proportion of CAP is associated with respiratory viral infections. Determining the comprehensive etiology of respiratory viruses using conventional methods including viral culture, has been a challenge. These limitations were overcome in the present study through the use of sputum samples for the detection of viral and bacterial DNA as well as for conventional bacterial culture. Sputum samples have been rarely examined by PCR (27), probably because of the likelihood of sputum contamination with microbes in the upper respiratory tract. However, sputum is produced at the site of infection and is easily collected from patients in clinical settings; therefore, we believe that sputum samples are more reliable and sensitive than other samples such as nasopharyngeal swabs for lower respiratory tract viral infections (27). In addition, the results of PCR are less influenced by prior antimicrobial therapy (27). Although the consensus of definite clinical etiological significance has not been clearly defined for PCR-detected pathogens, we believe that multiplex-PCR assays for bacterial and viral DNA using sputum samples are useful in CAP epidemiological studies, particularly those conducted in resource-rich countries such as Japan.

The estimated overall incidence of adult CAP in Kochi, Japan (9.6 per 1,000 PY) is higher than that in other countries, which could be explained by several factors. First, the overall pneumonia incidence is influenced by the population structure. Japan has the fastest-growing aging population in the world; 22.1% and 10.3% of the population comprised individuals aged >65 and >75 years, respectively, in 2008. These figures are substantially higher than those of other countries in Asia (6.8% and 2.4% population aged >65 and >75 years, respectively), Western Europe (17.8% and 8.5% population aged >65 and >75 years, re-

spectively), and Northern America (12.8% and 6.2% population aged >65 and >75 years, respectively) (11). In the present study, the incidence of CAP among people aged ≥75 years was approximately 12 (or more) times higher than that among those aged 15–64 years, indicating that the burden of pneumonia increases with the population age. In fact, previous reports also reveal that age-group-specific incidence among the adult population increases with advancing age (3,4,6,28). Furthermore, if the age group-specific estimates are projected onto the Japanese population of 1980, where the proportions of people aged ≥65 and ≥75 years were 9.1% and 3.1%, respectively, the overall incidence of adult CAP would reduce to 5.1 per 1,000 PY. Therefore, our incidence estimates after age structure adjustment are comparable with those with other settings. Second, the definition of pneumonia varies between studies; certain studies have used CXR findings to determine pneumonia, whereas others have used clinically defined criteria or simply counted the number of hospitalized pneumonia cases (6,29). In our study, pneumonia was carefully defined using a standardized criteria based on CXR findings. Third, accessibility to health care differs between countries. In Japan, >70% of the medical costs for adults is covered by insurance because of universal health insurance coverage (12); therefore, there is limited impact of the barrier to hospital cares on estimates in our study. Moreover, almost all CAP patients were hospitalized, with severe clinical conditions; the incidence estimates in the present study are therefore likely to be the minimum values.

The present study has certain limitations. First, a single-center study is prone to selection bias and the included patients may not be representative of all CAP patients in Japan. However, there is a near absence of a barrier to health care access among CAP patients in Japan; moreover, the study was conducted in a typical Japanese rural city, where the proportion of elderly people is comparable with the Japanese average. As a result, the findings of the present study can be reasonably generalized. Second, serological tests for atypical bacterial pathogens were not performed. However, the impact of this limitation on the findings is likely negligible because the sensitivity of PCR assays for atypical pathogens is comparable with that of serological tests (17). Third, the enrollment rate of the prospective survey was relatively low (41%). However, the age and sex of prospectively and retrospectively enrolled patients were similar (data not shown); the pattern of associated pathogens described in the present study can therefore be assumed to be substantially representative. Fourth, the number of CAP patients identified from the ICD-10 coded database was employed for incidence estimates, and certain CAP cases may have been missed owing to miscoding. In addition the ratio of the number of patients with CAP to the total number of outpatients with other diseases was assumed to be constant across all hospitals in the city, and this assumption may be debatable; however, to the best of our knowledge, a better practical method is not available. Further investigations, including a multicenter study, are warranted for the verification of this assumption.

Despite the above mentioned limitations, our study clearly demonstrated that the incidence of adult CAP

among the Japanese population was high, probably reflecting the substantial aged population. The disease burden is likely to further increase as the population ages. This situation may also arise in other Asian countries because their populations are also rapidly aging (11). Effective vaccination strategies for *S. pneumoniae*, *H. influenzae*, and respiratory viruses must therefore be considered for elderly people.

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