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Original Article

Serotype distribution of *Streptococcus pneumoniae* isolated from adult respiratory tract infections in nationwide Japanese surveillances from 2006 to 2014

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ABSTRACT

Background and objective: Reports on the efficacy of pneumococcal conjugate vaccines (PCVs) have been received from many countries. However, in countries where the 7-valent PCV (PCV7) and 13-valent PCV (PCV13) were introduced, overall coverage of the serotypes by the vaccine gradually decreased due to pneumococcal serotype replacement. The aim of this study is to assess the distribution of pneumococcal serotypes and to also provide basic data on adult respiratory infection in Japan.
Methods: We analyzed 1086 *Streptococcus pneumoniae* strains that had been isolated from respiratory tract infection specimens in adult patients from 2006 to 2014. Capsular typing was performed by the Quellung reaction and multiplex PCR.
Results: Among all 1086 strains, serotype 3 was the most common and was identified in 160 strains (14.7%), followed by serotypes 19F, 6B, 19A and 23F. From 2006–10 to 2012–14, the coverage rate of PCV7 tended to gradually decrease. Particularly, serotypes 6B and 19F of penicillin non-susceptible strains decreased. On the other hand, serotypes 19A and 15A of penicillin non-susceptible strains increased. However, coverage by PCV13 of penicillin-resistant *S. pneumoniae* (PRSP) (penicillin G minimum inhibitory concentration ≥2 μg/mL) remained high (88.7% [2006–10], 88.0% [2012–14]).
Conclusions: In Japan, PCV13 vaccination of adults became available from June 2014. Our study demonstrated that most PRSP (88.0%) still remain covered by PCV13. At present, the introduction of PCV13 in adult clinical practice seems to be highly significant. However, there is a possibility that the distribution has been changing, and careful screening should be continued in the future.

1. Introduction

Despite remarkable progress in the clinical practice for the treatment of pneumonia, the disease remains the third leading cause of death in Japan [1]. The most important factor related to this phenomenon is the super aging of society, as pneumonia deaths are particularly rapidly increasing among elderly people. There are also no practical solutions to address other factors like inflating medical costs, an increasing number of antimicrobial-resistant bacteria and the slow development of new antimicrobial agents [2,3].

Streptococcus pneumoniae (*S. pneumoniae*) is one of the major pathogens that cause pneumonia, it also causes serious invasive diseases like meningitis and septicemia in all age groups [2,3]. Therefore, pneumococcal vaccination is considered an effective preventive method against pneumococcal infections [4]. Since 2000, the 7-valent pneumococcal conjugate vaccine (PCV7: serotypes 4, 6B, 9V, 14, 18C, 19F, 23F) has been used to vaccinate children in the United States, and presently the 10-valent pneumococcal conjugate vaccine (PCV10: serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F) and the 13-valent pneumococcal conjugate vaccine (PCV13: serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 23F) are administrated to both adults and children in more than 100 countries. In Japan, children have been immunized with PCV7 since 2010 and with PCV13 since 2013. Although pneumococcal polysaccharide vaccine 23 (PPV23), which contains 23 types of capsular

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antigen, has conventionally been given to adults, PCV13 has become available for adult use since June 2014. There have been reports on the efficacy of PCVs from many countries, as represented by a significant reduction in invasive pneumococcal diseases (IPDs) in children [5–7]. Accordingly, pneumococcal infections in adults have also decreased as an indirect effect of the widespread use of PCVs for children [8,9]. However, in countries where PCV7 or PCV13 was introduced, overall coverage of serotypes by the vaccine gradually decreased due to pneumococcal serotype replacement from the vaccine type to non-vaccine types such as 6C, 15A, 23A, and 35B [10–13].

The Japanese Society of Chemotherapy (JSC) established a nationwide surveillance network of the antimicrobial susceptibility of bacterial respiratory pathogens in 2006 and has conducted surveillance in collaboration with the Japanese Association for Infectious Diseases (JAID) and the Japanese Society for Clinical Microbiology (JSCM) [14–16]. We confirmed the serotypes of *S. pneumonia* that cause adult respiratory tract infections through our nationwide surveillance. The aim of this study is to assess the distribution of pneumococcal serotypes and also to provide basic data to assess changes in their distribution after the introduction of PCV13 to adults in Japan.

2. Materials and methods

2.1. Study design

Five nationwide studies conducted under the initiative of JSC, JAID and JSCM were conducted in 2006, 2008, 2010, 2012 and 2014 [14–16]. The numbers of participating hospitals in each study are shown in Table 1. In previous reports, all institutions use a same diagnostic criteria based on Three Academic Societies Joint Antimicrobial Susceptibility Surveillance program, each study included all pneumococcal isolates collected from respiratory samples of adults [14–16].

2.2. Streptococcus pneumoniae isolates

We obtained 1086 *S. pneumoniae* strains from the 2006 to 2014 surveillances. The strains of well-diagnosed adult respiratory tract infection were isolated from sputum and specimens of transtracheal aspiration or bronchoscopy. Their causality was confirmed by quantitative culture, Gram staining, and observation of phagocytes [2]. Table 1 shows the kinds of specimens, patient characteristics, diagnosis and susceptibility to penicillin. All strains were grown on Sheep Blood Agar® (Nippon Beckton-Dickinson, Tokyo, Japan) and were maintained at 35 °C with 5% CO_2. The strains were stored in a Microbank™ system (IWAKI, Tokyo, Japan) at −80 °C.

2.3. Susceptibility testing

The bacterial susceptibility to penicillin G (PCG) was studied using the broth microdilution method. The reference broth microdilution method was performed according to the Clinical Laboratory Standard Institution guidelines [17–19]. The test medium was prepared using cation-adjusted Mueller–Hinton broth (Eikenkagaku, Tokyo, Japan) with lysed horse blood (Nippon Biotest Laboratory, Tokyo, Japan). Microtiter plates were then inoculated to produce a final inoculum density of approximately 5×10^5 CFU/mL, which was regularly controlled by counting the colonies. The inoculated plates were incubated at 36 °C for 20–24 h before interpreting the results. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of antibiotics that inhibited bacterial growth. Strains with PCG MIC ≤0.06 μg/mL were classified as penicillin-susceptible *S. pneumoniae* (PSSP), those with PCG MIC of 0.12–1 μg/mL as penicillin-intermediate *S. pneumoniae* (PISP), and those with PCG MIC ≥2 μg/mL as penicillin-resistant *S. pneumoniae* (PRSP) [18].

2.4. Capsular typing

Capsular typing was performed by the Quellung reaction and multiplex PCR. The Quellung reaction was performed using a set of antisera obtained from Statens Serum Institute (Copenhagen, Denmark). The typing procedure was performed as described in the previous report [20]. Multiplex PCR was performed based on the procedure of the Streptococcus Laboratory in the Center for Disease Control and Prevention [21]. The PCRs were performed on 25 μl volumes, and each reaction mixture contained the following: 2× PCR buffer (QIAGEN Multiplex PCR Kit, Germany) 12.5 μl, clinical sample of 5 μl DNA, and primers with the concentrations specified in the protocol published by the Centers for Disease Control and Prevention.

Table 1
Details of the specimens in this study by each year.

Characteristics	Total	Year				
		2006	2008	2010	2012	2014
Number of isolates	1086	200	211	189	225	261
Participating hospitals		35	46	34	39	42
Source of isolates						
Sputum (%)	947 (87.2)	190 (95.0)	187 (88.6)	158 (83.6)	193 (85.7)	219 (83.9)
Trans-tracheal aspiration (%)	104 (9.6)	6 (3.0)	17 (8.1)	22 (11.6)	24 (10.7)	35 (13.4)
Bronchoscopy (%)	23 (2.1)	2 (1.0)	5 (2.4)	5 (2.7)	6 (2.7)	5 (1.9)
Others[a] (%)	12 (1.1)	2 (1.0)	2 (0.9)	4 (2.1)	2 (0.9)	2 (0.8)
Patient characteristics						
Age, median (interquartile range)	73 (61–79)	72 (62–80)	71 (61–80)	78 (58–78)	72 (63–79)	72 (63–80)
Sex, men (%)	716 (65.9)	142 (71.0)	142 (67.3)	123 (65.1)	150 (66.7)	159 (60.9)
Community-acquired pneumonia (%)	717 (66.0)	124 (62.0)	141 (66.8)	119 (63.0)	159 (70.7)	174 (66.7)
Hospital-acquired pneumonia (%)	105 (9.7)	26 (13.0)	22 (10.4)	21 (11.1)	18 (8.0)	18 (6.9)
Acute exacerbation of chronic bronchitis (%)	136 (12.5)	27 (13.5)	26 (12.4)	27 (14.3)	23 (10.2)	33 (12.6)
Others[b] (%)	128 (11.8)	23 (11.5)	22 (10.4)	22 (11.6)	25 (11.1)	36 (13.8)
Minimum inhibitory concentration of penicillin						
≤0.06 μg/mL (%)	607 (55.9)	122 (61.0)	111 (52.6)	81 (42.9)	144 (64.0)	149 (57.1)
0.12–1 μg/mL (%)	392 (36.1)	70 (35.0)	75 (35.5)	79 (41.8)	70 (31.1)	98 (37.5)
≥2 μg/mL (%)	87 (8.0)	8 (4.0)	25 (11.8)	29 (15.3)	11 (4.9)	14 (5.4)

[a] Biopsy, unknown.
[b] Aspiration pneumonia, healthcare associated pneumonia, others.