

## Factors associated with pneumococcal vaccine uptake in elderly subjects referred to the respiratory department

Keisuke Watanabe<sup>1,2</sup>, Yoshihito Asai<sup>2</sup>, Naomi Tsurikisawa<sup>2</sup>, Chiyako Oshikata<sup>2</sup>,  
and Takeshi Kaneko<sup>1</sup>

<sup>1</sup>Department of Pulmonology, Yokohama City University Graduate School of Medicine, Yokohama, Japan  
<sup>2</sup>Department of Respiratory Medicine, Hiratsuka City Hospital, Hiratsuka, Japan

### ABSTRACT

*Streptococcus pneumoniae* is the most common pathogen for community-acquired pneumonia and is also common in nursing and healthcare-associated pneumonia. Pneumococcal vaccine shows clinical benefit and 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been introduced in a routine immunization program in Japan. However, uptake of PPSV23 remains low, at 40%. One opportunity for capturing unvaccinated subjects is hospital referrals. Identifying factors associated with pneumococcal vaccination among referred subjects is thus important so that pulmonologists can maximize the capture of unvaccinated subjects. We retrospectively reviewed the records of subjects with a first referral to the Department of Respiratory Medicine at Hiratsuka City Hospital from September 2017 to March 2018. Subjects who were  $\geq 65$  years old and lived in Hiratsuka were included in this study. We compared the backgrounds of subjects and investigated factors associated with pneumococcal vaccination. A total of 142 individuals were included in this study and the pneumococcal vaccination rate was 44.4% (95% confidence interval (CI), 36.0–52.9%). Of these, 127 subjects regularly visited clinics and/or hospitals for any diseases and their pneumococcal vaccine rate was 44.1% (95%CI, 35.3–53.2%). In multivariate analysis, chronic respiratory diseases (odds ratio 5.7; 95%CI, 2.2–14.9,  $P < 0.001$ ) and receipt of PPSV23 notification (odds ratio 8.5; 95%CI, 2.5–29.0,  $P < 0.001$ ) were positively associated with pneumococcal vaccination. In conclusion, chronic respiratory diseases and receipt of PPSV23 notification were positively associated with pneumococcal vaccination. However, pneumococcal vaccination rates remain relatively low, even in subjects regularly visiting clinics and/or hospitals.

Keywords: *Streptococcus pneumoniae*, Pneumococcal vaccine, 23-valent pneumococcal polysaccharide vaccine, community-acquired pneumonia

#### Abbreviations:

CAP: community-acquired pneumonia

IPD: invasive pneumococcal disease

PPSV23: 23-valent pneumococcal polysaccharide vaccine

PCV13: 13-valent pneumococcal conjugate vaccine

This is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Received: January 27, 2020; accepted: February 3, 2020

Corresponding Author: Keisuke Watanabe, MD, PhD

Department of Pulmonology, Yokohama City University Graduate School of Medicine, 3-9 Fukuura,  
Kanazawa-ku, Yokohama 236-0004, Japan

Tel: +81-45-352-7962, Fax: +81-45-352-7963, E-mail: YCUmedRDckw@yahoo.co.jp, watanabk@yokohama-cu.ac.jp

## INTRODUCTION

Pneumonia is one of the leading causes of death in Japan. In addition to being a major direct cause of death, pneumonia increases the risks of long-term morbidity and mortality,<sup>1</sup> deterioration of cognitive function<sup>2</sup> and declines in physical function.<sup>3</sup> *Streptococcus pneumoniae* is the most common pathogen underlying community-acquired pneumonia (CAP)<sup>4</sup> and is also common in nursing and healthcare-associated pneumonia.<sup>5</sup> In addition to pneumonia, *S. pneumoniae* can cause invasive pneumococcal disease (IPD), which shows high mortality rates of 11–30% in developed countries.<sup>6</sup> Two kinds of pneumococcal vaccine are available for *S. pneumoniae* in Japan: 23-valent pneumococcal polysaccharide vaccine (PPSV23); and 13-valent pneumococcal conjugate vaccine (PCV13). Both PPSV23 and PCV13 have clinical benefit to the elderly. PPSV23 reduces the risk of IPD,<sup>7</sup> pneumococcal pneumonia (although controversy remains regarding the effects on pneumonia)<sup>8,9</sup> and death from any cause in hospitalized CAP.<sup>10</sup> PCV13 reduces the risk of pneumococcal CAP and IPD.<sup>11</sup> Recently, PPSV23 has been introduced to routine immunization programs for the elderly in Japan. Uptake of PPSV23 has increased, but is still low, at only 40%.<sup>12</sup> One of the chances for capturing unvaccinated elderly individuals is when they are referred to hospital, as the proportion of eligible subjects is high in hospital settings.<sup>13</sup> Identifying the factors associated with pneumococcal vaccination among referred elderly subjects is important to increase the uptake of pneumococcal vaccine. The factors associated with pneumococcal vaccination in the general population<sup>14–17</sup> and immunosuppressed patients<sup>18,19</sup> have been reported. However, information about factors associated with pneumococcal vaccination in referred subjects remains limited. We retrospectively reviewed the records of subjects who were referred to the department of respiratory medicine at a tertiary-care hospital and investigated factors associated with pneumococcal vaccination, so that clinicians could better capture unvaccinated elderly individuals.

## PATIENTS AND METHODS

This study was conducted at Hiratsuka City Hospital, a tertiary-care hospital with 416 beds located in Hiratsuka, in the middle part of Kanagawa Prefecture in Japan.

We retrospectively reviewed the records of those subjects referred to the Department of Respiratory Medicine at Hiratsuka City Hospital for the first time from 28 September, 2017 to 1 March, 2018. All subjects who visited our department for the first time were routinely asked if they had received pneumococcal vaccination.

Subjects who were  $\geq 65$  years old and lived in Hiratsuka were included in this study. Subjects for whom data were lacking were excluded. Uptake of pneumococcal vaccine was self-reported. We compared the backgrounds of subjects and investigated factors contributing to the uptake of pneumococcal vaccine.

In Japan, the national vaccination program for pneumococcal vaccine started in 2014. Individuals turning 65, 70, 75, 80, 85, 90, 95 or 100 in the fiscal year are eligible for municipal subsidies. Only PPSV23 is supported by this program. Hiratsuka City joined this program and started subsidies from 2014. All citizens have since been receiving notifications from Hiratsuka City by mail when they become eligible.

Data are presented as median and range unless otherwise specified. EZR version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan)<sup>20</sup> was used for all statistical analyses. Comparisons were made using the t test or Mann-Whitney U test for continuous variables. Categorical variables were compared with Pearson's chi-square test or Fisher's exact test. Multivariate

analysis was performed by logistic regression analysis for factors showing values of  $P < 0.15$  in univariate analysis. Statistical significance was set for values of  $p < 0.05$ , and all tests were 2-tailed.

This study was approved by the institutional review board at Hiratsuka City Hospital (approval no. 29-086). Due to the retrospective nature of this study, the need to obtain written informed consent was waived.

## RESULTS

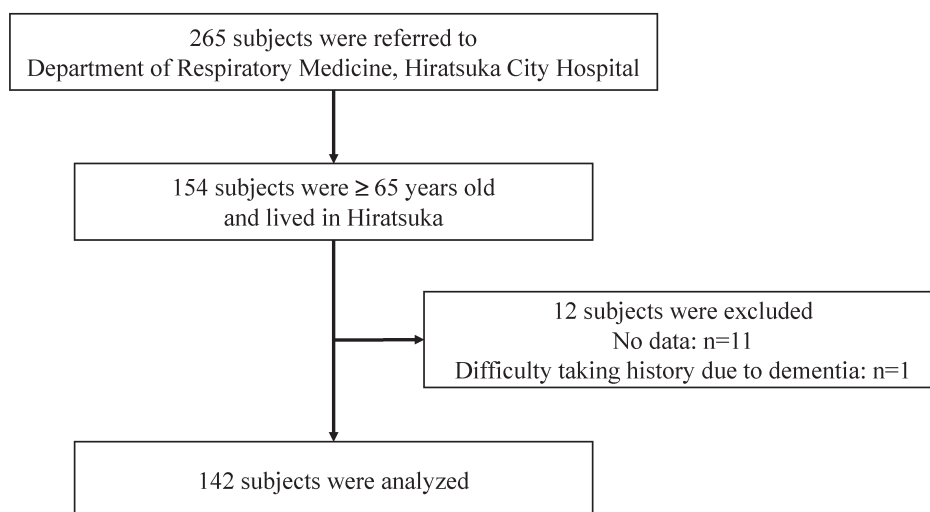
Figure 1 shows the flow diagram of the study. A total of 265 individuals were referred to our department between 28 September, 2017 and 1 March, 2018. Among these, 154 subjects were  $\geq 65$  years old and lived in Hiratsuka. Of these 154 subjects, 12 were excluded (11 due to lack of data, 1 for whom history was difficult to elicit due to dementia). Finally, data from 142 subjects were analyzed in this study.

Table 1 shows subject characteristics. Median age was 76 years (range, 65–99 years) and 78 subjects were male. Seventy individuals were past smokers, 10 were current smokers. Regular visits to clinics and/or hospitals for any disease and for internal diseases were reported for 89.4% and 83.1% of subjects, respectively.

The pneumococcal vaccination rate was 44.4% (63/142; 95% confidence interval (CI), 36.0–52.9%) in all subjects, 44.1% (56/127; 95%CI, 35.3–53.2%) among those who regularly visited clinics and/or hospitals for any diseases, and 43.2% (51/118; 95%CI, 34.1–52.7%) among those who regularly visited clinics and/or hospitals for internal diseases.

Table 2 shows a comparison of subjects with and without pneumococcal vaccination. In vaccinated subjects, frequencies of chronic respiratory disease and receipt of notification of PPSV23 from the municipality were higher than in those without vaccination. Sex and use of systemic steroids and/or immunosuppressants also tended to differ between groups, but the differences were not significant.

Logistic regression analysis was performed for chronic respiratory diseases, receipt of PPSV23 notification, sex and use of systemic steroids and/or immunosuppressants. Chronic respiratory



**Fig. 1** Flow diagram of the study

**Table 1** Background characteristics of subjects (n=142)

Sex, female:male	64:78
Age, years	76 [65–99]
Smoking history (current/ex/never)	10/70/62
Pneumococcal vaccination	63 (44.4%)
Comorbidities	
Chronic respiratory disease <sup>a</sup>	36 (25.4%)
Cardiovascular disease <sup>b</sup>	27 (19.0%)
Collagen vascular disease <sup>c</sup>	5 (3.5%)
Diabetes	24 (16.9%)
Active malignancy	5 (3.5%)
Regularly visiting clinics and/or hospitals for	
Any disease	127 (89.4%)
Internal disease	118 (83.1%)
Use of systemic steroid and/or immunosuppressant	5 (3.5%)
Receipt of PPSV23 notice from municipality	110 (77.5%)
Reason to visit our hospital (radiographic abnormality <sup>d</sup> )	62 (43.7%)
Definitive diagnosis	
COPD and/or emphysema	17 (12.0%)
Chronic lower respiratory tract infection	16 (11.3%)
Lung cancer <sup>e</sup>	14 (9.9%)
Pneumonia	9 (6.3%)
Asthma	6 (4.2%)
Interstitial lung disease	5 (3.5%)
Other disease <sup>f</sup>	22 (15.5%)
No newly diagnosed lung disease <sup>g</sup>	47 (33.1%)
Unknown <sup>h</sup>	6 (4.2%)

Data are presented as median [range] or number of patients (%), unless otherwise specified. COPD: chronic obstructive pulmonary disease.

<sup>a</sup> Chronic respiratory diseases include chronic obstructive pulmonary disease, asthma, interstitial lung disease, old pulmonary tuberculosis and bronchiectasis.

<sup>b</sup> Cardiovascular diseases include old myocardial infarction, angina pectoris, valvular diseases, congestive heart failure, aortic aneurysm, peripheral artery diseases.

<sup>c</sup> Collagen vascular diseases include rheumatoid arthritis, Sjögren's syndrome and antineutrophilic cytoplasmic antibody-associated vasculitis.

<sup>d</sup> From annual lung cancer screening or medical check.

<sup>e</sup> Metastatic lung cancer is included (renal cell carcinoma, n=1; breast cancer, n=1).

<sup>f</sup> Other diseases included ground-glass nodules under follow-up (n=4), pleural plaque (n=3), chronic bronchitis (n=2), heart failure (n=2), pneumothorax (n=2), post-infectious cough (n=2), tuberculosis (n=2), acute bronchitis (n=1), bronchiectasis (n=1), pulmonary arteriovenous malformation (n=1), pulmonary hypertension (n=1) and thymoma (n=1).

<sup>g</sup> Subjects referred to our hospital because of abnormal shadow on annual lung cancer screening or medical check, but showing no lesion or only old inflammatory change on chest computed tomography.

<sup>h</sup> Subjects with lung opacity that improved spontaneously (n=4), hemoptum of unknown cause (n=1) or loss to follow-up (n=1).

**Table 2** Comparison of patients with and without pneumococcal vaccination

	Pneumococcal vaccination (+) (n=63)	Pneumococcal vaccination (-) (n=79)	P
Age, years	76 (65–91)	76 (66–99)	0.990
Sex (female:male)	33:30	31:48	0.130
Smoking history (never/past+current)	31/32	31/48	0.307
Comorbidities			
Chronic respiratory disease	26 (41.3%)	9 (11.5%)	<0.001
Cardiovascular disease	15 (23.8%)	12 (15.2%)	0.205
Collagen vascular disease	1 (1.6%)	4 (5.1%)	0.382
Diabetes	11 (17.5%)	13 (16.5%)	1.000
Active malignancy	3 (4.8%)	2 (2.5%)	0.655
Regularly visiting clinics and/or hospitals for:			
Any disease	56 (88.9%)	71 (89.9%)	1.000
Internal disease	51 (81%)	67 (84.8%)	0.653
Use of systemic steroid and/or immunosuppressant	0 (0%)	5 (6.3%)	0.066
Receipt of PPSV23 notice from municipality	59 (93.7%)	51 (64.6%)	<0.001
Reason for visiting our hospital (radiographic abnormality <sup>a</sup> )	26 (41.3%)	36 (45.6%)	0.615

Data are presented as median (range) or number of patients (%).

<sup>a</sup> From annual lung cancer screening or medical check

**Table 3** Logistic regression analysis for factors associated with pneumococcal vaccination

	odds ratio [95%CI]	P
Chronic respiratory diseases	5.7 [2.2–14.9]	<0.001
Receipt of PPSV23 notice from municipality	8.5 [2.5–29.0]	<0.001
Sex (male)	0.7 [0.3–1.4]	0.305
Use of systemic steroid and/or immunosuppressant	–	0.988

diseases (odds ratio 5.7; 95%CI, 2.2–14.9, P<0.001) and receipt of PPSV23 notice (odds ratio 8.5; 95%CI, 2.5–29.0, P<0.001) were positively associated with pneumococcal vaccination (Table 3).

## DISCUSSION

In this study, pneumococcal vaccination rates were 44.4% and 44.1% in all referred elderly subjects and in referred elderly subjects under treatment for any diseases, respectively. Chronic respiratory diseases and receipt of PPSV23 notification were positively associated with pneumococcal vaccination.

Multivariate analysis showed that subjects with chronic respiratory diseases were more likely to undergo pneumococcal vaccination. This is in accordance with previous studies in the general population<sup>14-17</sup> and immunosuppressive patients.<sup>18,19</sup> Christenson et al showed that the pneumococcal vaccination rate was higher among subjects with chronic lung diseases in the Swedish general

population.<sup>14</sup> Among rheumatoid arthritis patients, the presence of lung disease was associated with recommendation for pneumococcal vaccination by physicians.<sup>18</sup> However, other diseases such as diabetes, rheumatoid arthritis and cardiovascular diseases increase the risk of CAP.<sup>21</sup> In addition, even age increases the risk of CAP.<sup>21</sup> However, vaccination rates in subjects with any diseases or internal diseases were unsatisfactory. In this study, 89.4% of subjects regularly visited clinics and/or hospitals for any diseases, but the vaccination rate was only 44.1%. Even among subjects who regularly visited clinics and/or hospitals for internal diseases, only 43.2% were vaccinated. All doctors should recommend pneumococcal vaccination to their patients  $\geq 65$  years old, as advice from a family physician increases the uptake of pneumococcal vaccine<sup>15</sup> and the main reason stated by unvaccinated subjects with rheumatoid arthritis or inflammatory bowel disease is absence of a recommendation from their physician or healthcare professionals.<sup>18,19</sup>

Subjects who were eligible for the subsidy and received notification from the municipality were also more likely to be vaccinated. This is in accordance with a previous study by Shono et al, who reported that eligibility for subsidies is related to uptake of pneumococcal vaccination.<sup>16</sup> However, even among subjects who received notification, the vaccination rate remains unsatisfactory (53.6%). Better knowledge about vaccination and recommendations are positively associated with vaccine uptake.<sup>19,22-24</sup> Notification with informative explanations might help increase vaccine uptake.

We excluded subjects living outside of Hiratsuka. Public subsidies for vaccination differ among local municipalities and larger public subsidies significantly elevate vaccination rates.<sup>25</sup> We could thus exclude the effect of this difference by focusing on subjects in Hiratsuka.

This study had some limitations. First, the retrospective design meant we could not analyze some potential confounding factors, such as recommendations from family physicians and socio-economic status. In particular, as mentioned above, absence of a recommendation from their physicians was negatively associated with vaccine uptake. Collecting such data is difficult in a retrospective study. Other factors in this study were taken from face-to-face interviews, which might have improved the reliability of responses. Second, we included subjects with pneumonia, and vaccination rates in pneumonia and other diseases might differ. Referral for pneumonia was not found to be related to vaccination uptake in this study (data not shown). However, correlations might become apparent if such a study included a larger number of subjects. Third, uptake of pneumococcal vaccine was self-reported. Self-reports are known to overestimate vaccination rates.<sup>26</sup> However, the vaccination rate in this study was roughly the same as the rate reported for Japan.<sup>12</sup> Fourth, we only asked about uptake of pneumococcal vaccine, not uptake of each pneumococcal vaccine (PPSV23 or/and PCV13). Prospective studies are thus warranted to confirm our findings.

In conclusion, chronic respiratory diseases and receipt of PPSV23 notification from the municipality were positively associated with pneumococcal vaccination in referred elderly individuals. However, the pneumococcal vaccine rate was relatively low in referred elderly subjects, although most were regularly visiting clinics and/or hospitals. All doctors should recommend pneumococcal vaccination to patients  $\geq 65$  years old. Clinicians should check if the referred patients have received pneumococcal vaccination, even if they regularly visit clinics and/or hospitals for chronic diseases.

#### ACKNOWLEDGEMENT

None.

## CONFLICT OF INTEREST

Takeshi Kaneko received research grant and/or lecture fees from Pfizer and MSD.

## REFERENCES

1. Eurich DT, Marrie TJ, Minhas-Sandhu JK, et al. Ten-year mortality after community-acquired pneumonia: a prospective cohort. *Am J Respir Crit Care Med.* 2015;192(5):597–604. doi: 10.1164/rccm.201501-0140OC.
2. Shah FA, Pike F, Alvarez K, et al. Bidirectional relationship between cognitive function and pneumonia. *Am J Respir Crit Care Med.* 2013;188(5):586–592. doi: 10.1164/rccm.201212-2154OC.
3. Kato T, Miyashita N, Kawai Y, et al. Changes in physical function after hospitalization in patients with nursing and healthcare-associated pneumonia. *J Infect Chemother.* 2016;22(10):662–666. doi: 10.1016/j.jiac.2016.06.005.
4. Kurai D, Sasaki Y, Saraya T, et al. Pathogen profiles and molecular epidemiology of respiratory viruses in Japanese inpatients with community-acquired pneumonia. *Respir Investig.* 2016;54(4):255–263. doi: 10.1016/j.resinv.2016.01.001.
5. Noguchi S, Mukae H, Kawanami T, et al. Bacteriological assessment of healthcare-associated pneumonia using a clone library analysis. *PLoS One.* 2015;10(4):e0124697. doi: 10.1371/journal.pone.0124697.
6. Drijckoningen JJ, Rohde GG. Pneumococcal infection in adults: burden of disease. *Clin Microbiol Infect.* 2014;20(Suppl 5):45–51. doi: 10.1111/1469-0691.12461.
7. Jackson LA, Janoff EN. Pneumococcal vaccination of elderly adults: new paradigms for protection. *Clin Infect Dis.* 2008;47(10):1328–1338. doi: 10.1086/592691.
8. Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against community-acquired pneumonia in the general population aged  $\geq 60$  years: 3 years of follow-up in the CAPAMIS study. *Clin Infect Dis.* 2014;58(7):909–917. doi: 10.1093/cid/ciu002.
9. Suzuki M, Dhoubhadel BG, Ishifuji T, et al. Serotype-specific effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumococcal pneumonia in adults aged 65 years or older: a multicentre, prospective, test-negative design study. *Lancet Infect Dis.* 2017;17(3):313–321. doi: 10.1016/S1473-3099(17)30049-X.
10. Fisman DN, Abrutyn E, Spaude KA, et al. Prior pneumococcal vaccination is associated with reduced death, complications, and length of stay among hospitalized adults with community-acquired pneumonia. *Clin Infect Dis.* 2006;42(8):1093–1101. doi: 10.1086/501354.
11. Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med.* 2015;372(12):1114–1125. doi: 10.1056/NEJMoa1408544.
12. Naito T, Yokokawa H, Watanabe A. Impact of the national routine vaccination program on 23-valent pneumococcal polysaccharide vaccine vaccination rates in elderly persons in Japan. *J Infect Chemother.* 2018;24(6):496–498. doi: 10.1016/j.jiac.2018.01.004.
13. Di Nardo F, Calabrò GE, Iannuale C, et al. Capturing the chance for pneumococcal vaccination in the hospital setting. *Ann Ist Super Sanita.* 2017;53(4):291–298. doi: 10.4415/ANN\_17\_04\_04.
14. Christenson B, Lundbergh P. Comparison between cohorts vaccinated and unvaccinated against influenza and pneumococcal infection. *Epidemiol Infect.* 2002;129(3):515–524. doi: 10.1017/s095026880200780x.
15. Higuchi M, Narumoto K, Goto T, et al. Correlation between family physician's direct advice and pneumococcal vaccination intention and behavior among the elderly in Japan: a cross-sectional study. *BMC Fam Pract.* 2018;19(1):153. doi: 10.1186/s12875-018-0841-3.
16. Shono A, Hoshi SL, Kondo M. The impact on vaccination coverage following introduction of a routine pneumococcal vaccination programme for the elderly in Japan. *Vaccine.* 2018;36(39):5886–5890. doi: 10.1016/j.vaccine.2018.08.023.
17. Murakami Y, Kanazu S, Petigara T, et al. Factors associated with PPSV23 coverage among older adults in Japan: a nationwide community-based survey. *BMJ Open.* 2019;9(7):e030197. doi: 10.1136/bmjopen-2019-030197.
18. Hua C, Morel J, Ardouin E, et al. Reasons for non-vaccination in French rheumatoid arthritis and spondyloarthritis patients. *Rheumatology (Oxford).* 2015;54(4):748–750. doi: 10.1093/rheumatology/keu531.
19. Loubet P, Verger P, Abitbol V, et al. Pneumococcal and influenza vaccine uptake in adults with inflammatory bowel disease in France: results from a web-based study. *Dig Liver Dis.* 2018;50(6):563–567. doi: 10.1016/j.dld.2017.12.027.
20. Kanda Y. Investigation of the freely-available easy-to-use software “EZR” (Easy R) for medical statistics.

- Bone Marrow Transplant.* 2013;48(3):452–458. doi: 10.1038/bmt.2012.244.
21. Torres A, Peetermans WE, Viegi G, et al. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax.* 2013;68(11):1057–1065. doi: 10.1136/thoraxjnl-2013-204282.
  22. Klett-Tammen CJ, Krause G, Seefeld L, et al. Determinants of tetanus, pneumococcal and influenza vaccination in the elderly: a representative cross-sectional study on knowledge, attitude and practice (KAP). *BMC Public Health.* 2016;16:121. doi: 10.1186/s12889-016-2784-8.
  23. Loubet P, Kernéis S, Groh M, et al. Attitude, knowledge and factors associated with influenza and pneumococcal vaccine uptake in a large cohort of patients with secondary immune deficiency. *Vaccine.* 2015;33(31):3703–3708. doi: 10.1016/j.vaccine.2015.06.012.
  24. Sakamoto A, Chanyasanha C, Sujirarat D, et al. Factors associated with pneumococcal vaccination in elderly people: a cross-sectional study among elderly club members in Miyakonojo City, Japan. *BMC Public Health.* 2018;18:1172. doi: 10.1186/s12889-018-6080-7.
  25. Naito T, Matsuda N, Tanei M, Watanabe Y, Watanabe A. Relationship between public subsidies and vaccination rates with the 23-valent pneumococcal vaccine in elderly persons, including the influence of the free vaccination campaign after the Great East Japan Earthquake. *J Infect Chemother.* 2014;20(7):450–453. doi: 10.1016/j.jiac.2014.03.004.
  26. Jiménez-García R, Hernandez-Barrera V, Rodríguez-Rieiro C, et al. Comparison of self-report influenza vaccination coverage with data from a population based computerized vaccination registry and factors associated with discordance. *Vaccine.* 2014;32(35):4386–4392. doi: 10.1016/j.vaccine.2014.06.074.