Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: https://www.tandfonline.com/loi/khvi20

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To cite this article: Ezgi Demirdogen Cetinoglu, Esra Uzaslan, Abdullah Sayıner, Aykut Cilli, Oguz Kılınc, Aysın Sakar Coskun, Armağan Hazar, Nurdan Kokturk, Ayten Filiz, Mehmet Polatli & on behalf of TURCAP Study Group (2017) Pneumococcal and influenza vaccination status of hospitalized adults with community acquired pneumonia and the effects of vaccination on clinical presentation, Human Vaccines & Immunotherapeutics, 13:9, 2072-2077, DOI: 10.1080/21645515.2017.1339851

To link to this article: https://doi.org/10.1080/21645515.2017.1339851

Published online: 25 Jul 2017.

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HUMAN VACCINES & IMMUNOTHERAPEUTICS
2017, VOL. 13, NO. 9, 2072–2077
https://doi.org/10.1080/21645515.2017.1339851

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RESEARCH PAPER

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Pneumococcal and influenza vaccination status of hospitalized adults with community acquired pneumonia and the effects of vaccination on clinical presentation

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ABSTRACT

Background: Previous reports have shown that vaccination rates of adult at-risk populations are low in Turkey. There are differing reports with regards to the effectiveness of the influenza and the pneumococcal polysaccharide vaccine (PPSV23) on the clinical outcomes of community acquired pneumonia (CAP). The purpose of this study was to analyze the influenza (FV) and pneumococcal vaccination (PV) status, the factors that influence the receipt of influenza/pneumococcal vaccine and the effects of prior vaccination on the clinical outcomes in adults hospitalized with CAP. **Patients and Methods**: Patients hospitalized with CAP between March 2009 and October 2013 and registered at the web-based Turkish Thoracic Society Pneumonia Database (TURCAP) were included in this multicentric, observational study. Of a total of 787 cases, data were analyzed for 466 patients for whom self-reported information on PV and FV was available. **Results**: In this adult population with CAP, the vaccination rate with both the pneumococcal and influenza vaccines was found to be 6%. Prior FV was found to be the sole variable that was associated with the receipt of PV [OR 17.8, 95% CI (25–75:8.56–37.01), $p < 0.001$]. Conversely, being vaccinated with PPSV23 was the only predictor of receipt of FV [OR 18.1, 95% CI (25 – 75:8.75 – 37.83), $p < 0.001$]. Compared to the unvaccinated cases, the chest radiograms of the vaccinated patients revealed less consolidation. The latter also reported fatigue, muscle pain and gastrointestinal symptoms less frequently. Although there was a trend for lower 30-day mortality and for lower rates of intensive care unit (ICU) admission, these did not reach statistical significance. A pneumonia severity index (PSI) score $\geq$ 90, CURB-65 score $\geq$3 and multilobar involvement, but not the vaccination status, were identified as independent determinants of ICU admission. **Conclusions**: This study showed that, among patients hospitalized with CAP, the FV and/or PV rates are low. Prior vaccination does not appear to significantly affect the clinical outcomes.

ARTICLE HISTORY
Received 16 February 2017
Revised 15 May 2017
Accepted 5 June 2017

KEYWORDS
adults; community-aquired pneumonia; influenza vaccination; pneumococcal polysaccharide vaccination; vaccination status

Introduction

Community acquired pneumonia (CAP) remains one of the primary health problems worldwide.[1,2] At least 20% of the patients necessitate hospitalization and mortality rates are especially high among the elderly and in cases that require intensive care.[3] Several societies, including the Turkish Thoracic Society (TTS), the European Respiratory Society (ERS), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the Advisory Committee on Immunization Practices (ACIP) have thus recommended pneumococcal vaccination for adults.[4-6]

Until recently, pneumococcal polysaccharide vaccine (PPSV23) was the only available pneumococcal vaccine in Turkey. The effectiveness of PPSV23 on the risk of developing CAP and on CAP-related mortality, however, are controversial. Several randomized controlled trials, cohort studies and a recent meta-analysis have shown PPSV23 to be non-effective in preventing the risk of developing CAP and in reducing the need for hospital admissions,[7-11] while in other studies, PPSV23 vaccination was associated with decreased rates of both pneumococcal CAP and all-cause CAP.[12-14] Besides, the polysaccharide vaccination has been found to be associated with more rapid improvement of symptoms, shorter hospital stay, reduced intensive care unit (ICU) admissions and reduced mortality rates in hospitalized CAP patients.[12,15-20]

Elderly patients and those with a chronic illness also carry a high risk for influenza infections and post-influenza pneumonia.[21] Influenza infections may increase susceptibility for

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pneumococcal infection by causing overexpression of pneumococcal binding receptors, impaired alveolar macrophage phagocytosis and neutrophil dysfunction.[22,23] National and international guidelines thus recommend annual immunization with influenza vaccine for individuals at high risk, including adults who are 65 y and older and those with chronic diseases.[4-6]

Despite guideline recommendations, previous studies have reported that the uptake of both the pneumococcal and influenza vaccinations is very poor in the adult population in Turkey.[24,25] The purpose of this observational study is to analyze the influenza and/or pneumococcal vaccination status of patients hospitalized with a diagnosis of CAP, the factors that influence the receipt of influenza/pneumococcal vaccine and the effects of vaccination on the clinical outcome of pneumonia. It also aims to investigate the effects of vaccination on ICU admission and on 30-day mortality rate in patients hospitalized with CAP.

Results

Of the 466 cases whose vaccination status were recorded in the database, 70% (n = 327) were male and the median age was 68 (18–94). The demographic, clinical and laboratory findings are summarized in Table 1. The most common presenting symptoms were, in order of frequency, cough (94%), fever (72%), fatigue (71%), and flank pain (43%). Altered consciousness was noted in 10%. A causative pathogen was identified in 56 (12.0%) of the patients and *S. pneumoniae* was the leading pathogen (n = 13, 23.2%).

Vaccination status and factors affecting vaccination

The rate of vaccination was low. There were 378 patients (81%) who had not received either vaccine, 45 patients (10%) were in the FV group, 13 (3%) in the PV group and 30 patients (6%) had received both vaccines. Although patients with comorbidities were more likely to have been vaccinated compared with patients with no comorbid conditions, their rate of vaccination remained low. None of the patients with chronic renal failure and chronic liver disease had received both vaccines (Table 2). Awareness was highest among patients with chronic obstructive pulmonary disease (COPD), of whom 13.6% had received both vaccines.

Logistic regression analysis of factors that may affect the receipt of pneumococcal vaccine showed that influenza vaccination was the only variable that was associated with pneumococcal vaccination [OR 17.8, 95% CI (25–75: 8.56–37.01), $p < 0.001$] (Table 3a). On the other hand, influenza vaccination was associated with pneumococcal vaccination [OR 18.1, 95% CI 8.75–37.83) and presence of comorbidities [OR 3.79, 95% CI 13.31) (Table 3b).

Effect of vaccination on the clinical presentation

Significant differences were observed between groups in age, some symptoms and radiological findings (Table 1, Table 4). Multinomial logistic regression analysis showed that patients who had received influenza vaccine reported fatigue and muscle pain less frequently than patients who had not been vaccinated (OR: 0.51, 0.27–0.97 and OR: 0.41, 0.18–0.96, respectively). Gastrointestinal symptoms were less frequently reported in patients who had received both vaccines. There was no difference among the groups regarding the rates the other symptoms were reported.

The radiologic findings are summarized in Table 4. Consolidation was observed less frequently in patients who had received either or both vaccines (OR: 0.43, 0.23–0.82; OR: 0.19, 0.06–0.62; OR: 0.27, 0.13–059, for the FV, PV and both-vaccine (BV) groups, respectively). There was no difference among the

Table 1. Demographic and clinical characteristics of the study population.

	NV (n = 378)	FV (n = 45)	PV (n = 13)	BV (n = 30)	P value
Age	67 (18–94)	71 (36–90)	76 (60–89)	70 (31–88)	0.002*
Residence- n %					0.410
House	370 (97.9%)	45 (100%)	13 (100%)	28 (93.3%)	
Nursing home	6(1.6%)	0 (0%)	0(0%)	2 (6,7%)	
Other	2 (0.5%)	0 (0%)	0(0%)	0(0%)	
Current/former smoker- n %	241 (64.1%)	31(70.5%)	9(69.2%)	20(66.7%)	0.838
Cough- n %	342 (%93.4)	44 (%97.8)	13 (%100)	28 (93.3%)	0.737
Fever- n %	250 (70.8%)	33 (73.3%)	12 (92.3%)	23 (76.7%)	0.352
Flank pain- n %	139 (43.2%)	21 (46.7%)	5 (%38.5)	13 (43.3%)	0.954
Fatigue- n %	254 (74,5%)	27(60%)	9(69,2%)	14(46,7%)	0.004†
Muscle pain - n %	98 (31.2%)	7 (15.9%)	1 (7.7%)	5 (17.2%)	0.027#
Headache- n %	62 (19.7%)	7 (15.6%)	2 (15.4%)	2 (6.7%)	0.325
GI symptoms- n %	72(22.9%)	11(25.6%)	3(23.1%)	0(0%)	0.029‡
Altered consciousness-n %	40 (10.6%)	3 (6.7%)	2 (15.4%)	3 (10%)	0.772
Systolic BP (mmHg)	120 (70–230)	120 (90–170)	110 (80–150)	120 (80–170)	0.059
Pulse rate/minute	98 (56–205)	90 (60–131)	96 (70–130)	93 (60–134)	0.375
Respiratory rate/minute	25 (12–48)	24 (16–42)	25 (20–30)	25 (16–38)	0.751
Body temperature (°)	37.7 (35.739.8)	38 (36–39)	38 (36–38.9)	38 (36–39.5)	0.295

Significant difference between PV and NV groups.
†*Significant difference between BV and NV groups.*
#*Although there was a significant difference between the four groups, no significant difference was observed in paired comparisons.*
‡*Significant difference between the BV group and the other three groups.*
Numerical values are given as median (min-max).
GI: gastrointestinal, BP: blood pressure

Table 2. Vaccination status according to comorbidities.

	NV (n = 378)	FV (n = 45)	PV (n = 13)	BV (n = 30)
Diabetes mellitus	75 (79.8%)	13 (13.8%)	1 (1.1%)	5 (5.3%)
Coronary artery disease	84 (82.4%)	10 (9.8%)	3 (2.9%)	5 (4.9%)
Cerebrovascular disease	29 (72.5%)	5 (12.5%)	2 (5%)	4 (10%)
Congestive heart failure	33 (73.3%)	9 (20%)	0 (0%)	3 (6.7%)
Chronic renal failure	13 (81.2%)	2 (12.5%)	1 (6.2%)	0 (0%)
Chronic liver disease	8 (88.9%)	1 (11.1%)	0 (0%)	0 (0%)
Asthma	20 (69%)	7 (24.1%)	0 (0%)	2 (6.9%)
Malignancy	29 (67.4%)	9 (20.9%)	3 (7%)	2 (4.7%)
COPD	94 (71.2%)	17 (12.9%)	3 (2.3%)	18 (13.6%)
Other	113 (82.5%)	12 (8.8%)	6 (4.4%)	6 (4.4%)
No comorbidity	66 (94.3%)	2 (2.9%)	1 (1.4%)	1(1.4%)

As most patients had more than one comorbidity, the numbers do not add up to 466. The data are presented as the number (%) of patients with the related comorbidity. COPD: chronic obstructive pulmonary disease

groups regarding the profusion of the infiltrates (unilateral vs bilateral and unilobar vs multilobar) and the presence of signs of complicated disease (abscess or pleural effusion).

Effect of vaccination on clinical outcomes

The length of hospital stay was similar among the 4 vaccination groups (Table 5). Twenty-nine of the patients were admitted to the ICU. There was no significant difference between the groups regarding the rate of ICU admission (Table 5). Logistic regression analysis showed that pneumonia severity index (PSI) class IV-V, CURB-65 score $\geq$ 3 and multilobar involvement were independent predictors for ICU admission (Table 6).

Table 3a. Independent correlates of receiving pneumococcal vaccine.

Variables for receipt of pneumococcal vaccine	No (%) of vaccinated patients	OR (95%CI)	P value
Age			0.306
$\geq$ 65 y	30 (69.8%)	1.49 (0.69–3.23)	
<65 y	13 (30.2%)	1.00 (ref.)	
Comorbidities			
Present	41 (95.3%)	1.82 (0.38–8.54)	0.447
Absent	2 (4.7%)	1.00 (ref.)	
Current/former smoker	29 (67.4%)	1.01 (0.47–2.18)	0.966
Non-smoker	14 (32.6%)	1.00 (ref.)	
Influenza vaccination			
Yes	30 (69.8%)	17.8 (8.56–37.01)	<0.001
No	13 (30.2%)	1.00 (ref.)	

Table 3b. Independent correlates of receiving influenza vaccine.

Variables for receipt of influenza vaccine	No (%) of vaccinated patients	OR (95%CI)	P value
Age			0.663
$\geq$ 65 y	49 (65.3%)	1.14 (0.62–2.07)	
<65 y	26 (18.4%)	1.00 (ref.)	
Comorbidities			
Present	71 (95.9%)	3.79 (1.08–13.31)	0.037
Absent	3 (4.1%)	1.00(ref.)	
Current/former smoker	51 (68.9%)	1.16 (0.63–2.14)	0.628
Non-smoker	23 (31.1%)	1.00(ref.)	
Pneumococcal vaccination			<0.001
Yes	30 (40%)	18.1 (8.75–37.83)	
No	45 (60%)	1.00(ref.)	

Table 4. Radiologic findings according to the vaccination status.

Chest X-ray	NV (n = 378)	FV (n = 45)	PV (n = 13)	BV (n = 30)	P value
Consolidation	287(%75.9)	26 (%57.8)	5 (%38.5)	14 (%46.7)	<0.001‡
Interstitial/patchy	135(%35.7)	28 (%62.2)	11(%84.6)	21(%70)	<0.001†
Cavitation	18 (%4.8)	2 (%4.4)	1 (%7.7)	0 (%0)	0.536
Multilobar involvement	67(%17.7)	11(%24.4)	4(%30.8)	7(%23.3)	0.425
Pleural effusion	71(%18.8)	4(%9.1)	0 (%0)	5(%16.7)	0.143

‡*The patients who had received neither vaccine (NV) were significantly more likely to present with consolidation on chest X-ray than the patients who had received both vaccines (BV) or the just pneumococcal vaccine (PV).*
†*The patients who had received neither vaccine (NV) had a lower frequency of interstitial/patchy infiltrates on chest X-ray than the patients who had received either or both vaccines.*

Table 5. Clinical outcomes in the 4 vaccination groups.

	NV (n = 378)	FV (n = 45)	PV (n = 13)	BV (n = 30)	P value
Length of hospital stay (days)	7 (2–55)	7 (2–23)	9 (3–20)	6 (2–21)	0.171
ICU admission (n)	25 (6.6%)	2 (4.4%)	1 (7.7%)	1 (3.3%)	0.802
30-day mortality (n)	18 (9.6%)	4 (22.2%)	2 (16.7%)	0 (0%)	0.258

Numerical values are given as median (min-max)
ICU: intensive care unit

The 30-day mortality data were available for 222 patients only. The mortality rate was 10.8% and there was no significant difference among the vaccination groups (Table 5).

Discussion

This study aimed to determine the influenza and pneumococcal vaccination status of patients hospitalized with CAP and whether previous immunization affects the clinical presentation and/or the clinical outcomes of these patients. In this study population which consisted of patients with moderate-to-severe CAP who were all admitted to a hospital, only 6% reported to have received both vaccines. Prior influenza vaccination was determined to be the single variable that influenced the receipt of pneumococcal vaccination. Vaccination was associated with

Table 6. Logistic regression analysis: Independent correlates for ICU admission in hospitalized patients with CAP.

Variables	OR (95%CI)	P value
Age $\geq$ 65 y	0.47 (0.18–1.20)	0.116
Age<65 y	1.00(ref.)	
Influenza vaccination administered	0.51 (0.12–2.14)	0.358
NOT administered	1.00(ref.)	
Pneumococcal vaccination administered	1.06 (0.19–5.91)	0.942
NOT administered	1.00(ref.)	
Presence of comorbidities	0.42 (0.11–1.64)	0.215
Absence of comorbidities	1.00(ref.)	
Current/former smoker	0.66 (0.28–1.59)	0.363
Non-smoker	1.00(ref.)	
PSI class IV-V	25.39 (2.78–231.64)	0.004
PSI class I-II-III	1.00(ref.)	
CURB-65 $\geq$ 3	3.66 (1.31–10.26)	0.013
CURB-65 < 3	1.00(ref.)	
Multilobar involvement	3.54 (1.42–8.80)	0.006
NOT Multilobar involvement	1.00(ref.)	

PSI: Pneumonia severity index

a lower frequency of fatigue, muscle pain and gastrointestinal symptoms at clinical presentation and of consolidation on chest X-rays. However, although the data were relatively limited, vaccination did not appear to affect the clinical outcomes.

This study confirmed previous reports that the rates of pneumococcal and influenza vaccination are low in Turkey.[24,26,27] The findings of this study reflect real-life data and it allowed us to identify an area where efforts should be directed. As the main determinant for receiving one of the vaccines is the receipt of the other, it appears that awareness drives vaccination. The barriers to adult immunization in Turkey and possible solutions have recently been addressed.[28]

Patients who had received influenza vaccine reported fatigue and muscle pain less frequently and those who had been immunized with both vaccines had less gastrointestinal symptoms, possibly suggesting that the influenza vaccination is effective in reducing the rate of infection with or the severity of symptoms due to the influenza virus.

Patients who had previously been vaccinated did not appear to have milder radiographic involvement at presentation. The extent of involvement and the presence of signs of complicated disease were similar in vaccinated as compared with unvaccinated cases. These findings are similar to those observed in a Spanish study.[18] The only significant difference was the lower frequency of consolidation. Although there is no strong association between the radiographic patterns and the causative agents,[29, 30] consolidation is more frequently observed in pneumococcal pneumonia.[31] Accordingly, the lowest rates of consolidation were observed in the PV and BV groups in this study, suggesting that pneumococcal vaccination may have had some preventive effect for pneumococcal pneumonia, or may have resulted in milder forms of radiographic presentation.

In accordance with previous studies,[6,32] *S. pneumoniae* was the leading pathogen in this population. However, the main limitation of this study was that causative bacteria were identified in a small minority (12%) of the patients. Besides, viruses were not routinely tested. Thus, it was not possible to make comparisons of the microbiologic findings among the vaccination groups. However, this was a real-life study and low identification rates are frequently encountered in such settings.

Several studies have addressed the efficacy of the influenza and pneumococcal polysaccharide vaccines. Influenza vaccination has been shown to reduce the rate of ICU admission, i.e. disease severity,[33] and mortality in the general population and in patients hospitalized for CAP.[34,35] On the other hand, other studies have not shown any difference in disease severity; the length of hospital stay was found to be shorter only in the younger age groups (50–64 years).[36] The pneumococcal polysaccharide vaccine has been found to reduce the rate of invasive pneumococcal disease, but its efficacy against all-cause pneumonia has been observed in low-income (OR 0.54, 95% CI 0.43 to 0.67) but not in high-income countries in the general population (OR 0.71, 95% CI 0.45 to 1.12).[7] Another meta-analysis showed that it was associated with a reduction in the rate of both all-cause pneumonia and presumptive pneumococcal pneumonia. However, the results were heterogeneous and, when the trials of higher methodologic quality were considered, there was no evidence of vaccine protection for pneumonia and of any reduction in mortality.[37] In patients hospitalized for CAP, prior vaccination with the polysaccharide vaccine was associated with a reduced need for intensive care.[17,20]

This study did not show any difference in clinical outcomes, although there were trends for lower rates of ICU admission and of 30-day mortality in the group who had received both vaccines. One important reason could be the low number of vaccinated patients. Analyzing the data from a larger population might have provided a clearer understanding of the effects of vaccination on the clinical outcomes. Another reason for the apparent lack of benefit could be the older age of the population. Although elderly people are one of the major risk groups for whom vaccination is recommended, their immune response to vaccination is weaker.[38]

ICU admission was associated with higher PSI and CURB-65 scores and multilobar involvement. Similarly, data from the same database showed that predictors of treatment failure, defined as clinical deterioration or death, were high PSI scores and low PaO_2/FiO_2 ratios.[39] These findings support previous reports that PSI score is a strong predictor of clinical outcome.[40,41]

The major strength of this study is that it has only concentrated in patients with pneumonia. Thus, it provides more detailed data on the effects of vaccination on the clinical presentation and outcome of CAP. Besides, it has provided insight into the uptake of vaccination in the at-risk groups and provided evidence regarding the importance of physician and patient awareness on the rate of immunization.

Beside those that have already been discussed, there are other limitations to this study. First, as this is not a randomized study, it is potentially prone, like any observational study, to selection bias and the existence of confounding factors. However, the probability of selection bias is low since the data was obtained from 9 individual reference centers that provide universal, independent public health service. Second, the immunization status was self-reported. There may have been errors in recall, particularly regarding the timing of the pneumococcal polysaccharide vaccine. When compared with medical records, self-reported pneumococcal and influenza vaccination status has high sensitivity, but, the specificity is low (38–46% for influenza and pneumococcal vaccinations, respectively).[42] Another limitation may be related to the decisions for admission to the ICU and for discharge from the hospital. As in any real-life setting, these were left at the discretion of the attending physicians and may have affected the reported clinical outcomes. Finally, these results reflect findings associated with the use of the pneumococcal polysaccharide vaccine and thus, cannot be generalized to the use of the conjugate vaccine.

In conclusion, this study showed that the vaccination rate among adults admitted to the hospital with CAP, mostly of older age groups and with comorbidities, was very low and that efforts should concentrate on raising awareness among the patients and physicians. Prior vaccination was associated with a lower rate of influenza-related symptoms. Although no statistical significance was detected, there was a trend for lower rates of ICU admission and of 30-day mortality in patients who had been immunized with both vaccines.

Patients and methods

CAP cases that were diagnosed in 5 separate geographical regions and 9 centers between March 2009 and October 2013

and registered at the web-based Turkish Thoracic Society Pneumonia Database (TURCAP) were included in this observational study.

The TURCAP database was established to collect epidemiological and clinical data on CAP in Turkey and included patients admitted to 9 medical centers. These 9 centers (which also contributed their data to this study) are from 5 of 7 geographical regions of the country and thus, the study population can be considered to be representative of the general population. The main aims of the project are to facilitate clinical research at the national level, to evaluate the processes of care and the clinical outcomes, and ultimately, to improve the management and outcomes of CAP. Thus, all investigators are encouraged to include all consecutive patients and required to complete standard case report forms at admission and during follow-up. The patients are followed up by their attending physicians who prospectively collect the data and record them in the database. All consecutive patients who meet the inclusion and exclusion criteria are registered into the database. The accuracy of the data are checked by the principal investigator at each site. The TURCAP Project is supported by a grant from the TTS.

The diagnosis of pneumonia was made in all cases with the presence of relevant symptoms, physical examination findings and of infiltrates on their chest roentgenograms[5] Past medical history and vaccination status of patients were recorded by experienced physicians. Of the 787 cases from 9 tertiary care centers, information on PPSV23 (PV) and influenza vaccination (FV) were recorded for 466 patients and these formed the study population. At admission, all patients were asked about their vaccination status. They were considered to be vaccinated if they had received one dose of influenza vaccine for the related season (the preceding fall) or one dose of PPSV23 during the preceding 5 years. The pneumococcal conjugate vaccine became commercially available for adults in 2011, but was not reimbursed by the national insurance system during the study period. Thus, all patients included in this study received the polysaccharide vaccine. Since the quadrivalent influenza vaccine was unavailable in Turkey before 2014, all patients received the trivalent influenza vaccine.

The cases were divided into 4 groups: those vaccinated with both PV and FV (BV), those vaccinated with just PV or FV and those who had not received either vaccine (NV). Demographic, clinical, laboratory and radiological findings at admission as well as data on the clinical outcomes, intensive care requirement and mortality were retrieved for all cases and comparisons were made between the 4 groups.

Statistical analyses

All statistical analyses were performed with IBM SPSS ver.23.0. Shapiro Wilk test was used as normality test. Continuous variables were compared using Mann-Whitney U test and Kruskal Wallis test when the data were not normally distributed. Categorical variables were compared using Pearson's chi-square test, Fisher's exact test and Fisher-Freeman-Halton test. Evaluation of the relative variables to vaccination was performed by multinomial and binary logistic regression model. A p-value < 0.05 was considered as significant.

The TURCAP Study Group also included the following investigators: Sezai Tasbakan, MD, Burcu Karaboğa, MD, Öznur Kilic, MD, Yavuz Havlucu, MD, Fatma Tokgöz, MD, Sakine Nazik, MD.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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