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RESEARCH PAPER

Determinants of influenza vaccination among solid organ transplant recipients attending Sicilian reference center

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ABSTRACT

Among solid organ transplant recipients, influenza infection is commonly associated with higher morbidity and mortality than immunocompetent hosts. Therefore, in these subjects influenza vaccination is of paramount importance. The main objective of the study was to assess compliance to vaccination and analyze factors associated with influenza vaccination of solid organ transplant recipients admitted to the Sicilian solid organ transplant Reference Center IRCCS-ISMETT in Palermo during 2014–2015 influenza season. Thirty one (37.8%) out of 82 solid organ transplant recipients were vaccinated against influenza. The main reason for vaccination refusal was fear of adverse reaction (n = 16, 31.4%), impaired health status (n = 14, 27.4%) and low vaccine efficacy (n = 10, 19.6%). Vaccinated solid organ transplant recipients compare with unvaccinated had smaller hospital admissions for infectious respiratory diseases (9.7% Vs 23.5%) during surveillance period. On multivariate analysis the factors positively associated with influenza vaccination were the advice of Reference Center physicians (OR 53.4, $p < 0.001$) and to perform vaccine against pneumococcus (OR 7.0, $p = 0.016$). This study showed that Reference Center physicians play a key role on vaccine communication and recommendation for patients at risk and it underlines the effectiveness of influenza vaccination in solid organ transplant recipients. However, it remains that, although physician advice resulted a strong determinant for vaccination, influenza vaccination coverage in this subset of population remains still unsatisfactory.

KEYWORDS

counselling; determinants; healthcare workers; immunization factors; immunocompromised; influenza; pneumococcus; solid organ transplant; vaccine; vaccination uptake

Introduction

Influenza is a considerable public health issue due to its dissemination and contagiousness, causing annually 3 to 5 million cases of severe illness and 1 million deaths worldwide.[1] This disease is more serious in hospital setting, where healthcare workers are at increased risk of influenza, both for exposure to infected patients and viruses present outdoor.[2] Indeed, influenza attack rate varies between 5–10% in general population whereas 11–59% in healthcare workers who take care of patients with ILI.[3] Because influenza is more severe among patients with chronic diseases National Health Authorities identified at risk groups, including SOT recipients, to which recommend anti-influenza and anti-pneumococcal vaccination.[4,5,6,7] In particular IDSA guidelines counselled to administer inactivated influenza vaccine since one month after transplantation during community influenza outbreak.[8] Indeed influenza is even more common among SOT recipient as showed in a 10-year longitudinal study with an incidence of 4.3 cases per 1,000 person years.[9] In addition to complications (pneumonia and low airways infections) of general population, influenza can cause transplant rejection in SOT recipients.[9] Despite wide dissemination of guidelines among healthcare workers, vaccination against influenza is not yet standard practice in transplant centers. According to Dinits-Pensy et al.[10] many nephrological practices are reluctant to administer vaccines, partly due to a lack of understanding regarding their risk/benefit ratio. Slightly different results were found among heart transplant centers. Of the 28 transplant centers investigated in a multicenter study by White-Williams et al.[11] 25 recommended influenza vaccination. The remaining 3 centers did not recommend influenza vaccination because of a supposed association with allograft rejection. Furthermore, little is known about predictors of vaccine uptake in SOT recipients. With the exception of Berben et al.[12] that founded positive vaccination status significantly related to older age in a population of kidney transplant recipients.

The main objective of study was to analyze vaccination uptake and its determinants among SOT recipients to implement immunization adherence in a population at higher risk of influenza complications.

Result

A total of 82 SOT recipients were enrolled during the study period. Table 1 shows demographic and clinical characteristics of patients. Overall, the mean age was 50 y (CI 47–52),

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Table 1. Demographics and clinical characteristics of SOT recipients attending RC during 2014–2015 influenza season.

		Total N (%-IQR)	Vaccinated against influenza (n = 31), N (%-IQR)	Unvaccinated against influenza (n = 51), N (%-IQR)	p
Sex	Male	60 (73.2)	26 (43.3)	34 (56.7)	0.088
	Female	22 (26.8)	5 (22.7)	17 (77.3)	
Age		49.8 (46.6–52.0)	53.6 (48.6–50.5)	47.5 (43.4–51.6)	0.063
Country of origin	Italian	79 (96.3)	31 (39.2)	48 (70.8)	0.169
	Other	3 (3.7)	0 (0)	3 (100)	
School level	Nothing	3 (3.7)	2 (66.4)	1 (33.3)	0.128
	Primary	23 (28.0)	11 (47.8)	12 (52.2)	
	Secondary	27 (32.9)	12 (44.4)	15 (55.6)	
	College	19 (23.2)	3 (15.8)	16 (84.2)	
	University	10 (12.2)	3 (30.0)	7 (70.0)	
Employment status	Employed	40 (48.8)	8 (20.0)	32 (80.0)	0.004
	Retired	31 (37.8)	18 (58.1)	13 (41.9)	
	Unemployed	11 (13.4)	5 (45.5)	6 (54.5)	
Smoking habits	Never	43 (52.4)	12 (27.9)	31 (71.1)	0.132
	Not for 10 y	16 (19.6)	7 (43.7)	9 (56.3)	
	Yes	23 (28.0)	12 (52.2)	11 (47.8)	
ILI for 3 last seasons	Yes	35 (42.7)	8 (22.8)	27 (77.2)	0.016
Source of information about influenza vaccination	General Practitioner	29 (35.4)	12 (41.4)	17 (58.6)	0.022
	Reference center physician	19 (23.2)	16 (84.2)	3 (15.8)	
	Parents/friends	4 (4.9)	2 (50.0)	2 (50.0)	
	Other physician	5 (6.1)	1 (20.0)	4 (80.0)	
Vaccination against pneumococcus	Yes	17 (20.7)	11 (64.7)	6 (35.3)	0.010
Performed transplant	Liver	34 (41.5)	13 (38.2)	21 (61.8)	0.653
	Heart	9 (11.0)	4 (44.4)	5 (55.6)	
	Heart and kidney	1 (1.2)	0 (0)	1 (100)	
	Lung	22 (26.8)	9 (40.9)	13 (59.1)	
	Kidney	15 (18.3)	4 (26.7)	11 (73.3)	
	Liver and kidney	1 (1.2)	1 (100)	0 (0)	
Medical history	Bronchopulmunary diseases	26 (31.7)	13 (50.0)	13 (50.0)	0.121
	Cardiovascular diseases	60 (73.2)	24 (40.0)	36 (60.0)	0.498
	Diabetes	25 (30.5)	10 (40.0)	15 (60.0)	0.786
	Chronical renal failure	25 (30.5)	8 (32.0)	17 (68.0)	0.473
	Immunosuppressive diseases	1 (1.2)	0 (0)	1 (100)	0.433
	Chronic hepatitis	31 (37.8)	12 (38.7)	19 (61.3)	0.895
	Leukemia/lymphoma	3 (3.7)	0 (0)	3 (100)	0.169
	Solid tumor	9 (11.0)	4 (44.4)	5 (55.6)	0.663
	Other diseases	51 (62.2)	18 (35.3)	33 (64.7)	0.548

employed were more represented (48.8%) followed by retired from work (37.8%) and males were more recurring than females (73.2% Vs. 26.8%). Only 31 out of 82 (37.8%) performed vaccination against-influenza. More than half of SOT recipients (57.3%) declared to have not suffered from ILI during 3 previous influenza seasons. Moreover seventeen patients (20.7%) received anti-pneumococcal vaccination. The most frequently graft performed was liver (41.5%) followed by lung (26.8%) and kidney (18.3%). SOT recipients resulted suffering more from cardiovascular diseases (73.2%) followed by chronic hepatitis (37.8%) and chronic renal failure (30.5%).

Those who performed anti-influenza vaccination were older (53.6 Vs 47.5 years, respectively; $p = 0.063$), and more frequently retired from work than non-vaccinated ones (58.1% Vs 41.9%). On the other hand unvaccinated SOT patients were more recurrent than vaccinated employed (80.0% Vs. 20%) and unemployed (54.5% Vs 45.5%; $p = 0.004$). Furthermore, who suffered from ILI during the 3 previous seasons investigated, were significantly more resistant to anti-influenza vaccination (77.2% Vs 22.8%; $p = 0.016$). Comparing vaccinated with unvaccinated SOT recipients the main source of information in support of vaccination was RC physician (84.2% Vs. 15.8%), whereas General Practitioner (41.4% Vs. 58.6%) and other physician (20% Vs. 80%) resulted less effective ($p = 0.022$). The type of graft and medical history did not seem to influence the choice to be vaccinated against influenza among SOT recipients.

All factors significantly associated with anti-influenza vaccination adherence on bivariate analysis were included in a multivariate logistic analysis (Table 2). Supporting anti-influenza vaccination by RC physician (OR of 53.4; $p < 0.001$), followed by have been previously vaccinated against pneumococcus (OR 7.0; $p = 0.016$) were the main positively determinants of influenza vaccination among SOT recipients.

Table 2. Multivariate analysis of factors associated with influenza vaccine uptake among SOT recipients during 2014–2015 influenza season.

	OR	95% CI	
Sex (Male Vs. Female)	2.5	0.5	12.0
Age (per year increase)	1.0	0.9	1.1
Worker (Yes Vs. No)	0.4	0.1	2.5
Retired (Yes Vs. No)	1.3	0.1	11.8
ILI for 3 previous seasons (Yes Vs. No)	0.4	0.1	1.3
Vaccination against pneumococcus (Yes Vs. No)	7.0	1.4	34.4
Influenza vaccination information by Reference Center physician (Yes Vs. No)	53.4	7.2	394.8
Influenza vaccination information by General Practitioner (Yes Vs. No)	4.6	0.9	22.9

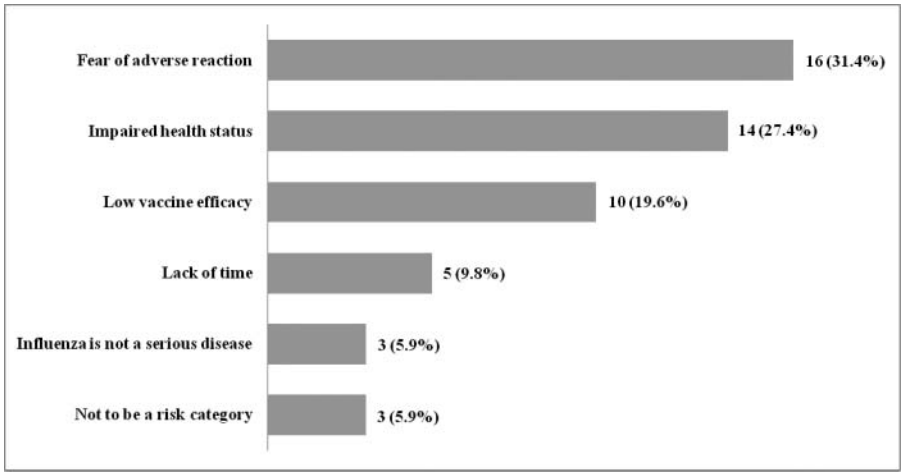

Figure 1. Reasons for missed vaccination in SOT recipients.

Figure 1 shows the causes of missed influenza immunization by SOT recipients. Among these, the fear of adverse reactions (31.4%) followed by health status (27.4%) and low vaccine efficacy (19.6%) played a major role.

Figure 2 shows the effectiveness of influenza vaccination analyzing the number of SOT recipients with at least one admission for respiratory diseases in season 2014–2015. Those who were not vaccinated had greater percentage of hospitalizations for respiratory disease compare with vaccinated (23.2% Vs. 9.7%; $p = 0.116$).

Discussion

This study analyzes the determinants of anti-influenza vaccination in a major "at risk" category as SOT recipients. Vaccination coverage in 2014–2015 season, in Italy, showed a slight decrease, with respect to previous season, both among general population (13.6%) and at risk categories like over 65 (48.6%).[13] In our series, observed values were lower in comparison with those reported by other studies conducted in SOT recipients.[14,15]

Overall, the key determinant for anti-influenza vaccination uptake was information provided by RC physician. According to our data, the suggestion of RC physician weighted more than General Practitioner, parents/friends and other sources. This could be explained by the general persuasion about more specific awareness of specialists about vaccine recommendations in this specific population.[14] This result makes us reflect on the need for continuous updating of physician especially those treating critical subjects as also suggested by our group in a previous paper about up to date knowledge on influenza epidemiology.[16]

Another factor positively associated with anti-influenza vaccination uptake among study population was to have had a previous experience of anti-pneumococcal vaccination (OR = 7.0; $p = 0.016$). The finding that, in adult population, a favorable opinion toward vaccination in general was associated with previous vaccination uptake of specific vaccines (influenza and pneumococcal) is worthy of interest. Similarly, Nichol et al.[17] also founded that positive attitudes toward immunization were independently associated with both influenza and pneumococcal vaccination behaviors among 700 immunocompromised adult patients.

The main reason for vaccination failure is fear of adverse events and in particular of graft rejection (data not shown in table). Because successful vaccination requires a partial activation of the immune system, doubts have been raised about a possible increase in the risk of acute rejection episodes, and thus about the safety of influenza vaccination in transplant patients.[11] This fear, however, has not been substantiated by scientific evidence.[6] Indeed rate of rejections did not increase in the months before, during, or after the administration of the influenza vaccine.[11] Another reason of missing vaccination was impaired state of health similarly to other studies conducted in

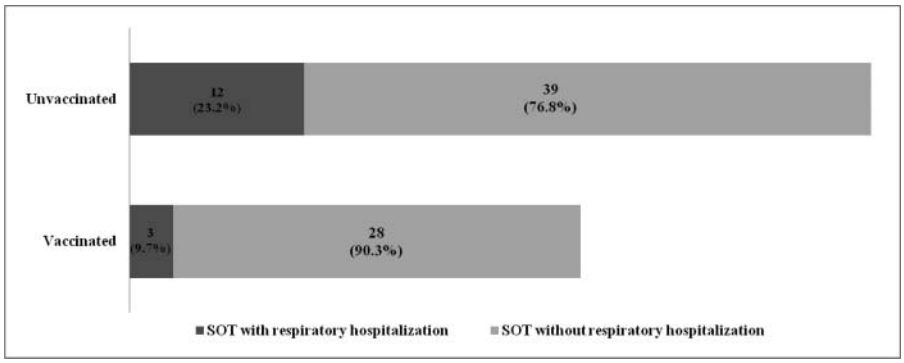

Figure 2. Following hospitalizations for respiratory disease among SOT recipients with or without performing anti-influenza vaccine during 2014–2015 influenza season.

the same area.[18,19] Among SOT recipients this belief can be attributed to the immunosuppressive therapy. Firstly it should be stressed that, if immunosuppressive therapy could partially decrease the immune system, it is true that to be exposed to microorganisms in real life should be much more at risk in respect of purified antigens contained in a vaccine. Subsequently, various studies have shown that SOT recipients antibody response to the influenza vaccine still significantly decreases the probability of contracting influenza.[20,21]

Monitoring SOT recipients admission to the Sicilian RC during influenza season there were a higher probability of health services request for respiratory diseases (pneumonia and low airways infection) among unvaccinated than vaccinated patients. This observation reveals an indirect proof of anti-influenza vaccine effectiveness. Other studies have found health benefits of anti-influenza vaccine in high-risk categories.[6,22] Even though further research is needed to evaluate the overall risks and benefits of anti-influenza-vaccine in SOT recipients.

Although the main limitation of study was the small sample analysis, the low number of donor in the area under investigation makes relevant obtained results.[23] Furthermore, the possibility of a recall bias during administration of the questionnaire may have been, although the use of electronic patient records, to obtain information about SOT recipients health conditions, should have reduced this risk.

In conclusion, this study underlines the need to improve the patient-doctor relationship at a communication level, especially in high risk patients concerning efficacy and safety of vaccination. Therefore, sharing detailed scientific knowledge among RC physician and General Practitioner will improve the awareness about vaccination safety and efficacy in general population, ultimately promoting health among at risk population as SOT recipients are.

Material and methods

This study was conducted with an observational design. Patients were enrolled from 42nd week of 2014 to 16th week of 2015 at IRCCS-ISMETT in Palermo (Sicilian SOT Reference Centre), an hospital with 78 beds for acute and 7 day hospitals taking care of 5,000 patients and performing a mean of 128 transplantation each year.[24] All SOT recipients or patients who performed a transplantation during hospital stay were administered a structured interview. Variables included in the questionnaire examined demographic characteristics (sex, age, occupation), health (smoking habits, medical history, type of graft) and vaccination status (anti-influenza and anti-pneumococcal vaccines). To investigate the effectiveness of anti-influenza vaccination it was registered patient with a hospital admissions for respiratory diseases among SOT recipients during all influenza season. This study was approved by the Institutional Review Research Board IRCCS-ISMETT.

Statistical analysis

All data were analyzed using Stata v14.1 statistical software. For all analyses, a p-value of 0.05 was assumed to indicate significance (2-tailed). Absolute and relative frequencies have been reported for qualitative variables, and medians (IQR) have been reported for quantitative, non-normally distributed variables. Normal distribution was verified by Shapiro Wilk's test for normality, and median data were compared using the Skewness and Kurtosis test. Categorical variables were analyzed using Chi square test (Mantel-Haenszel). All variables that were found to be significantly associated ($p < 0.05$) with influenza vaccination receipt in bivariate analysis were included in a multivariable logistic regression model. Goodness of fit was calculated for each model, and the model with the lowest Akaike Information Criterion was considered to have the best fit. Adjusted OR and CI 95% were calculated for the variables retained in the final model.

Abbreviations

CI	confidence intervals
IDSA	Infectious Diseases Society of America
ILI	influenza like illness
IQR	interquartile range
OR	odds ratio
RC	reference center
SOT	solid organ transplant

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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