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Attitudes, knowledge, and willingness to be vaccinated against seasonal influenza among patients hospitalized with Influenza-Like-Illness: impact of diagnostic testing

Sarah Tubiana (ST)^{a,b} Odile Launay (OL)^{c,d,e}, Florence Galtier (FG)^{e,f}, Pierre Tattevin (PT)^{e,g}, Deborah Postil (DP)^{e,h}, Philippe Vanhems (PVA)^{e,i}, Nezha Lenzi (NL)^e, Pierre Verger (PVE)^{e,j,k}, Xavier Duval (XD)^{a,b,e} and the Fluvac Study group

- a. Inserm CIC1425 Bichat, Hôpital Bichat-Claude Bernard, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France
- b. IAME, UMR1137, Sorbonne Paris Cité, F-75018 Paris, France
- c. Université Paris Descartes, Sorbonne Paris Cité, Inserm, CIC 1417, Paris, France, Paris, France
- d. Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Cochin, CIC Cochin Pasteur Paris, France
- e. Inserm, F-CRIN, Innovative clinical research network in vaccinology (I-REIVAC), Paris, France
- f. CIC 1411, Hôpital Saint-Eloi, CHU de Montpellier, Montpellier, France
- g. Hôpital Pontchaillou, INSERM U835, Faculté de Médecine, Université Rennes 1, IFR140, Rennes
- h. CIC de Limoges, CHU Dupuytren, Limoges, Limoges, France
- i. Service d'Hygiène, Epidémiologie et Prévention, Groupement Hospitalier Edouard Herriot, Lyon, and Emerging Pathogens Laboratory - Fondation Mérieux, Centre International de Recherche en Infectiologie (CIRI) Inserm U1111, CNRS UMR5308, ENS de Lyon, UCBL1, 69007 Lyon, France
- j. UMR VITROME (Vecteurs, Infections TROPicales et MEditerranéennes), Aix Marseille Univ, INSERM, IRD, Marseille, France
- k. ORS PACA, Observatoire Régional de la Santé Provence-Alpes-Côte d'Azur, Marseille, France

Corresponding author : Sarah Tubiana, Centre d'Investigation Clinique, CHU Hôpital Bichat-Claude Bernard, 46 Rue Henri Huchard, 75018 Paris, France ; Tel : +33140257148 ; Fax : +33140256776 ; e-mail adress : sarah.tubiana@aphp.fr

ABSTRACT

Influenza vaccine adherence remains low. Communication of virological diagnosis to adults hospitalized with influenza-like illness (ILI) could improve their willingness to be subsequently vaccinated. We prospectively assessed, in adults hospitalized with ILI in six French university hospitals, their willingness to be vaccinated against influenza in the subsequent season, both before and after the communication of RT-PCR Influenza laboratory result; we identified then the determinants associated with the willingness to be vaccinated.

A total of 309 patients were included during the 2012-2013 and 2013-2014 influenza seasons; 43.8% reported being vaccinated against influenza for the current season; before communication of influenza laboratory results, 65.1% reported willingness to be vaccinated during the subsequent season. Influenza was virologically confirmed in 103 patients (33.3%). The rate of vaccine willingness increased to 70.4% ($p=0.02$) after communication of influenza laboratory results. Factors independently associated with the willingness to be vaccinated were the perception of influenza vaccine benefits (adjusted relative risk (aRR): 1.06, 95%CI 1.02-1.10), cues to action (aRR: 1.08, 95%CI 1.03-1.12), current season influenza vaccination (aRR: 1.38, 95%CI 1.20-1.59) and communication of a positive influenza laboratory result (aRR: 1.18, 95%CI 1.03-1.34). This last was associated with the willingness to be vaccinated only in the subpopulation of patients not vaccinated (aRR: 1.53, 95%CI 1.19-1.96).

In patients hospitalized with ILI, communication of a positive influenza diagnostic led to a better appreciation of the disease's severity and increased the willingness to be vaccinated. This approach might be particularly beneficial in patients who do not have a history of influenza vaccination.

Keywords: Seasonal influenza vaccine, Influenza; Influenza-like illness, willingness

INTRODUCTION

Seasonal influenza is a major cause of morbidity-mortality worldwide, especially among the elderly and individuals with chronic underlying conditions[1–3]. According to the European Center for Disease Prevention and Control, approximately 40,000 Europeans die every year due to influenza [4]. Vaccination is the most effective strategy for preventing influenza infection and reducing related complications. In France, seasonal influenza vaccination is recommended annually for people more than 65 years old and for those belonging to populations at risk of poor influenza prognosis. Despite the efforts of primary care professionals and public health agencies, vaccine coverage remained close to 50% in the elderly and between 16% and 29% in the at risk population in 2015/16, far below the expected coverage rate of 75% [5,6]. To improve the coverage, it appears necessary to identify the determinants of influenza vaccination. Understanding which factors affect the acceptance of influenza vaccination would improve communication strategies.

Several studies analyzed the reasons for and/or barriers to acceptance of seasonal influenza vaccination in high-risk populations [7–14] and showed that it is largely driven by socio-demographic factors, the perceptions of the disease burden and of the vaccination risk-benefit balance. The Health Belief Model (HBM) is a widely used framework for investigating psychosocial determinants of health behaviors [15] and is recognized as a predictor of influenza vaccination uptake [16]. The HBM includes five constructs that influence health behaviors: perception of susceptibility, severity, barriers, benefits, and cues to action. Cues to action are strategies or information sources that promote adoption of a behavior. Individuals' perception of influenza disease susceptibility and severity is confused by the fact that several pathogens others than influenza are also involved in influenza-like illnesses (ILI), either of viral or bacterial origin, and that specific etiology often goes under-diagnosed. When an

influenza laboratory test is performed, the rate of influenza disease is only around 30-50% in general practice in patients with ILI during an influenza epidemic period [15]. Thus a heterogeneous group of diseases which are or are not influenza but share similar symptoms, may be perceived by patients as being influenza illnesses that should be effectively prevented by the influenza vaccine [14]. However little is currently known about attitudes and perceptions related to seasonal influenza vaccination among hospitalized patients with ILI with confirmed influenza disease.

We hypothesized that establishing with certainty the influenza diagnosis in hospitalized patients with ILI could modify perceptions of the influenza disease burden and risk-benefit balance of vaccination, modify health behaviors and improve acceptance of vaccination. In this context, we aimed to describe attitudes towards and knowledge of influenza disease and vaccination among hospitalized patients with ILI and to evaluate whether the communication of positive influenza laboratory result modifies patients' willingness to be vaccinated in the subsequent season.

METHODS

Study design and population

We performed an ancillary 'Social and Behavioral study' of the FLUVAC study. The FLUVAC study is a multicenter case-control design study conducted in 6 French university hospitals since the 2012-13 season which primarily aimed to evaluate influenza vaccine effectiveness in France among patients hospitalized with ILI [16]. Briefly, in the FLUVAC study, non-institutionalized adults patients (aged ≥ 18), hospitalized for at least 24 hours in one of the participating hospitals during the influenza epidemic periods, are systematically invited to participate in the study if they met the inclusion criteria (no contra-indication for

influenza vaccination and onset of ILI within 7 days prior to admission to hospital). All eligible patients who agreed to participate are interviewed and their nasopharyngeal swabs collected for centralized analysis. Influenza laboratory confirmation is obtained by RT-PCR on nasopharyngeal swabs.

All participants included in the FLUVAC study during the 2012-2013 and 2013-2014 seasons were then also invited to participate in the ancillary study divided into two successive steps: 1/ at inclusion, hereafter referred to as “pre-virological result questionnaire” and 2/at the end of the hospital stay when the result of influenza laboratory test was available, hereafter referred to as “post-virological result questionnaire”.

Ethics

The FLUVAC study (clinicaltrials.gov NCT02027233) was approved by regional ethics committees and all enrolled patients provided written informed consent before inclusion.

Data collection

Participants’ characteristic

Data were collected prospectively from hospital medical records and included demographics, background characteristics and in-hospital clinical evolution. Histories of influenza vaccination during the current season and each of the 2 preceding ones were registered as well as the source of this information.

Pre-virological result questionnaire

At the time of inclusion (i.e before nasopharyngeal swabs performance) a face-to-face 13-items structured questionnaire was administered to the participants. The questionnaire

contained 12 questions based upon the HBM which addressed participant's perception regarding vaccination (1 item), perception of influenza severity (1 item), perception of influenza vaccine benefits (3 items), barriers to the influenza vaccination (4 items) and cues to engage in the health behavior such as level of confidence in advice from a health care practitioner (3 items). The last question focused on participant's willingness to be vaccinated against influenza in the subsequent season.

Questionnaire wording and response scales are described in Supplementary material.

Post-virological result questionnaire

When available, the influenza laboratory result was given to the participant using the following sentence "laboratory test which have been performed on your nasopharyngeal swab established that you have had the flu" or "laboratory test which have been performed on your nasopharyngeal swab established that you did not have the flu" according to the situation. To evaluate whether it modified the willingness to be vaccinated, the post-result questionnaire was administered face-to face or by phone or sent by regular post in case of discharge. Taking into account influenza laboratory results, questions about perception of influenza severity and on the willingness to be vaccinated against influenza in the subsequent season were asked again of the participant.

Statistical analysis

Categorical variables were summarized using percentages and continuous variables were expressed using medians with interquartile ranges. Participant's perception regarding vaccination was re-coded in two categories (strongly against/against/don't know versus favorable/strongly favorable). Perception of influenza severity was categorized as "not severe" or "mildly severe" versus "moderate" or "highly severe". Internal scale reliability for

each cluster of modified HBM constructs statements (benefits of vaccination, barriers of vaccination and cues to action) was assessed using Cronbach's coefficient alpha. A value of >0.6 was considered indicative of acceptable internal scale reliability. All construct scores were analyzed as continuous scales. The willingness to be vaccinated against seasonal influenza in the subsequent season was scored dichotomously (Yes versus No/don't know).

Variables were compared before and after the communication of influenza laboratory test results using a McNemar's test. Firstly, we evaluated independent variables potentially associated with the willingness to be vaccinated against seasonal influenza (dependent variable) in the pre-virological result questionnaire and adjusted on location of participating hospitals and covariates previously described in the literature (sex, age, comorbidities and season of inclusion). Secondly, we evaluated factors associated with the willingness to be vaccinated against seasonal influenza as declared in the post-virological result questionnaire, adding into the model both the result of the laboratory test and the perception of influenza severity assessed in the post virological-result questionnaire. We estimated relative risks (RR) and 95% confidence intervals (95%CI), using multivariate Poisson regression model with robust variance. The lowest category of each variable was used as the reference group. Multicollinearity across all constructs was assessed. No variance inflation factor was greater than 10, and the mean of values was acceptable at 1.26 (pre-virological result model) and 1.22 (post-virological result model).

Statistical analyses were performed using the SAS software program (Version 9.2). A P-value $<.05$ was considered to indicate statistical significance.

RESULTS

Participants' characteristics

A total of 449 participants in 2012-2013 and 407 participants in 2013-2014 were included in the FLUVAC study. Among these 856 participants, 309 (36.1%) participated in the ancillary study: 144 (32.1%) in 2012-2013 and 165 (40.5%) in 2013-2014. Non-respondents were significantly older and had underlying disorders more often than those who responded to the ancillary study but they did not statistically differ from respondents in terms of sex, in-hospital clinical complications, current season vaccination status or influenza laboratory test result.

Main demographic and clinical characteristics of participants are listed in Table 1. Participants' median age was 61 years (interquartile range [IQR] 45-74 years), 51.8 % were male. Significant underlying disorders were reported in 236 participants (76.4 %) including respiratory diseases in 145 (46.9%), cardiac diseases in 91 (29.5%) and diabetes mellitus in 63 (20.4%) patients. Overall, 135/308 (43.8%) of participants with data available reported being vaccinated against influenza for the current season. According to the French immunization schedule, seasonal influenza vaccination was recommended for 258 (83.5%) of the 309 participants: among them, 127 (49.2%) reported being vaccinated for the current season.

In-hospital clinical complications occurred among 109 participants (35.3%) including pneumonia in 60 (19.4%), respiratory failure in 51 (16.5%), renal failure in 21 (6.8%) and cardiac failure in 15 (4.9%) participants.

Pre-virological result questionnaire

Overall, 249/304 (81.9%) participants with data available were favorable or strongly favorable to vaccination. Influenza was perceived as a moderate or highly severe disease for

89.8% of participants (272/303). Perceived benefits, perceived barriers to influenza vaccination and cues to engage in the health behavior are presented in Table 2.

A total of 201 participants (65.1%) reported willingness to be vaccinated against seasonal influenza in the subsequent season: 178 (88.6%) among those for whom seasonal vaccination was recommended.

In the fully adjusted model, factors independently associated with the willingness to be vaccinated against seasonal influenza in the pre virological-result questionnaire are presented in Table 3 a). Perception of influenza vaccine benefits and cues to action were associated with the willingness to be vaccinated while perception of barriers was significantly associated with decreased willingness to be vaccinated.

Influenza laboratory test results and post-virological result questionnaire

Among the 309 participants, 103 (33.3%) had laboratory-confirmed influenza. After communication of influenza laboratory test result, influenza was perceived as a moderate or highly severe disease for 92.1% of participants (279/303) (Table 2) with no significant difference between patients with laboratory-confirmed influenza (94.1%) and those with no laboratory-confirmed influenza (91.1%) ($p=0.50$). Compared to the pre-virological result questionnaire, there were no significant changes in the perception of influenza severity ($p=0.22$).

In the post-virological result questionnaire, 307 of the 309 participants answered to the question related to the willingness to be vaccinated. Of those 307 participants, 216 (70.4%) reported willingness to be vaccinated against seasonal influenza in the subsequent season, a rate which was significantly higher than those of the pre-result questionnaire ($p=0.02$).

Among the 258 participants for whom seasonal vaccination was recommended, 189 (73.3%) reported willingness to be vaccinated against seasonal influenza in the subsequent season. The rate of influenza vaccination willingness was 75.3% (76/101) in the subgroup of participants with a positive influenza laboratory result, and it was 68.0% (140/206) in those with a negative result ($p=0.19$).

Between the pre- and the post-virological result questionnaires, 38 patients modified their intention (12.3%); among them, 26 (68.4%) patients who initially did not plan to be vaccinated changed their intention and responded that they planned to be vaccinated in the post-result questionnaire: 15 patients with positive influenza laboratory result and 11 patients with negative influenza laboratory result. On the opposite, 12 patients (31.6%) who initially plan to be vaccinated changed their intention and responded that they planned not to be vaccinated in the post-result questionnaire: 4 patients with positive influenza laboratory result and 8 patients with negative influenza laboratory result.

Among patients with a negative influenza laboratory result ($n=205$), 136 (66.3%) reported willingness to be vaccinated against seasonal influenza in the pre-virological result questionnaire and 139 (67.8%) reported willingness to be vaccinated against seasonal influenza in the post-virological result questionnaire ($p=0.49$). Of the 136 patients with willingness to be vaccinated against seasonal influenza in the pre-virological result questionnaire, only 8 patients (5.9%) have modified their intention and planned not to be vaccinated in the post-result questionnaire.

Factors independently associated with the willingness to be vaccinated against seasonal influenza at the end of the hospital stay are presented in Table 3 b).

In the fully adjusted post-virological result model, an association was found between communication of a positive influenza laboratory test and the willingness to receive the influenza vaccine during the subsequent season (adjusted RR: 1.17, 95%CI 1.03-1.33). To better understand this relationship, we examined the model after stratification on current season influenza vaccine status. This showed that the willingness to be vaccinated was increased in case of positive influenza laboratory test only in the sub group of 173 patients not vaccinated (adjusted RR: 1.53, 95%CI 1.19-1.96), not in the 135 vaccinated patients (adjusted RR: 0.97, 95%CI 0.88-1.07) (Supplementary material Table S2).

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DISCUSSION

In this study conducted in France during the 2012-13 and 2013-14 influenza seasons in a population of hospitalized patients suspected of influenza illness, we assessed the willingness to be vaccinated during the subsequent season, and we identified associated factors before and after communication of influenza laboratory result. We showed that establishing influenza disease diagnosis significantly increased the willingness to be vaccinated, and this effect was particularly strong in individuals who reported not to be vaccinated for the current season.

Our study was a national prospective multicenter study, which included participants hospitalized in five university hospitals, and was conducted during two contiguous influenza seasons. Most patient characteristics were consistent with those reported in the literature among hospitalized patients with ILI, including predominance of chronic underlying conditions, a balanced sex ratio and a high proportion of current or past smokers [17]. The self-reported vaccine coverage was estimated at 43.8%, close to the French national estimate of about 50 % during the corresponding seasons for people older than 65 years old but higher than the influenza vaccine uptake estimate of 16% to 29% in people younger than 65 years with underlying conditions.

To correctly measure the impact of the influenza diagnosis on patients' willingness to be vaccinated, we sequentially questioned the patients before and after the communication of the influenza laboratory test. Before communication, the vaccination willingness rate for the subsequent season of 65.1% was higher than the self-reported vaccine coverage of 43.8% for the current season. This higher reported rate of vaccination willingness among our hospitalized patient population may be due to an acute perception of influenza severity and an increased awareness of their susceptibility related to their condition as hospitalized patients. This higher rate of influenza vaccination willingness is consistent with the rate of patients

favorable to the principle of general vaccination who had a high level of perception of the vaccine's benefits for themselves and the community, and who perceived seasonal influenza as a severe disease. This is also consistent with previous studies which found that elderly patients who did accept influenza vaccination reported a higher perceived severity and a higher perceived impact of its consequences [18–20].

Among the factors associated with the willingness to be vaccinated in both pre and post-virological result models, and consistent with other studies, the current season influenza vaccination status was the strongest factor associated with the willingness to be vaccinated in both pre and post-virological result models [21]. This reflects the stability of influenza vaccination attitudes and behaviours of individuals and therefore the difficulties in modifying vaccine acceptance in those who are reluctant. Consistent with findings based on self-reported vaccination or intention, we found that perception of benefits, barriers and cues to action were associated with the willingness to be vaccinated in the subsequent season [7].

The post-virological result questionnaire allowed us to analyze whether the communication of influenza laboratory test results (positive or negative) modified patient's willingness to be vaccinated, according to their current season influenza vaccination status. Identifying a link between influenza and their hospitalization increased patients' willingness to be vaccinated; this is consistent with previous results showing that a major reason to be vaccinated was the experience of getting very sick from influenza [23–25]. This result is not specific to influenza and was also found for instance in the context of pneumococcal vaccine, where a history of pneumonia was an independent factor associated with the willingness to receive a subsequent pneumococcal vaccine [26].

Interestingly, by stratifying the population by current season influenza vaccination status, we were able to identify that the willingness to be vaccinated was increased only in the stratum of

patients without seasonal influenza vaccination. In these patients, personal experience of having influenza is important in the decision-making process of vaccine acceptance. So far, these patients had not perceived themselves as susceptible to influenza infection. This underlines the importance of a laboratory test establishing the influenza diagnosis not only to prescribe specific antiviral and respiratory measures but also to improve the perception of influenza susceptibility and severity. The generalization of the rapid diagnostic tests may therefore be a relevant strategy to improve the evaluation of the risk-benefit balance of influenza vaccination in patients with ILI.

We acknowledge several limitations to our ancillary study. First, the participation rate of 36.1% was moderate. Second, we were not able to evaluate whether the intention to be subsequently vaccinated led in fact to a larger vaccination rate. Finally, the number of patients who modified their willingness to be vaccinated during the hospital stay was too low so that we could not analyze the factors associated with intent changes. Strengths of this study were enrollment of participants from six study sites to reduce the impact of geographical bias and render our results more generalizable and the use of an original methodology with influenza laboratory confirmation in a population of hospitalized patients suspected of influenza illness.

To conclude, determinants of influenza vaccination willingness are multiple and include the perception of the disease severity, which is influenced by the personal experience of influenza disease. Establishing with certainty the diagnosis of influenza may help clarify the perception of the disease, lead to a better evaluation of influenza disease severity and patients' susceptibility and might improve adherence to vaccination in individuals formerly reluctant to undergo vaccination.

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Author contributions:

Conception and design: OL, XD, PVE, ST.

Acquisition of data: OL, XD, PVE, PT, DP, NL, PVA, FG.

Statistical analysis and interpretation of data: ST, PVE, XD.

Drafting of the manuscript: ST, PVE, XD.

Critical revision of the manuscript for important intellectual content: OL, XD, PVE, ST, PT, DP, PVA, NL, FG.

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Transparency Declaration

XD, PVE, ST, PT, DP, PVA, NL and FG declare no competing interest related to the study.

OL reports grants from Sanofi Pasteur MSD during the conduct of the study.

Table 1: Descriptive characteristics of participants who responded to the Social and Behavioral's questionnaires, FLUVAC study 2012-2014 (N=309)

Variables	N	or % or IQR*
Demographics		
Season		
2012-2013 seasonal influenza	144	46.6
2013-2014 seasonal influenza	165	53.4
Location of participating hospitals		
Paris	238	77.0
Other	71	23.0
Age > 65 (years)	139	45.3
Male sex	160	51.8
Professional activity		
Working	95	30.7
Retired	155	50.2
Inactive	59	19.1
Medical history		
Smoking status		
Former	103	34.2
Current	67	22.3
Pregnancy	9	6.0
Underlying diseases		
≥ 1 comorbidity	236	76.4
Chronic respiratory disease	145	46.9
Chronic heart disease	91	29.5
Diabetes mellitus	63	20.4
Cancer	54	17.5
Immunosuppression	34	11.0
Chronic renal failure	31	10.0
Drepanocytosis or splenectomized	16	5.2
Neurological diseases	13	4.2
Cirrhosis	5	1.6
Indication for seasonal influenza vaccination	258	83.5
Current season influenza vaccination status		
No vaccination	173	56.2
Vaccination	135	43.8
In-hospital clinical evolution		
At least one complication**	109	35.3
Positive influenza laboratory test	103	33.3
Death	1	0.3

* IQR: Interquartile Range

** among pneumonia, respiratory, cardiac or renal failure, septic shock

Table 2: Attitudes towards influenza disease and vaccination in the Pre-and Post-result questionnaires, FLUVAC study 2012-2014 (N=309)

a) Pre-result questionnaire

Variables	Participants willing to be vaccinated (N = 201)		Participants not willing to be vaccinated (N=108)	
	N or Median	(%) or [IQR]IQR	N or Median	(%) or [IQR]
Perception of vaccination				
Favorable/strongly favorable	177	(88.5)	72	(69.2)
Strongly against/against/Don't know	23	(11.5)	32	(30.8)
Perception of influenza severity				
No or mildly severe disease	17	(8.5)	14	(13.6)
Moderate or highly severe disease	183	(91.5)	89	(86.4)
Perception of influenza vaccine benefits (Cronbach's $\alpha=0.86^*$)				
Individual prevention from catching seasonal influenza	2.0	[2.0;3.0]	1.5	[1.0;2.0]
Other people prevention from catching seasonal influenza	2.0	[2.0;3.0]	1.5	[1.0;2.0]
influenza vaccine present more advantages than risks	2.0	[2.0;3.0]	1.5	[1.0;2.0]
Perception of barriers to the influenza vaccination (Cronbach's $\alpha=0.60^*$)				
Painful of the influenza vaccination	0	[0;1.0]	1.0	[0;1.5]
Adverse effects caused by influenza vaccination	1.5	[0;2.0]	2.0	[1.5;3.0]
Influenza disease caused by influenza vaccination	1	[0;1.5]	1.5	[1.5;2.0]
Interferences with natural immune response	1.5	[0;1.5]	1.5	[1.0;1.5]
Cues to action (Cronbach's $\alpha=0.81^*$)				
Confidence in pharmaceutical firms	2.0	[1.5;3.0]	1.5	[1.0;2.0]
Confidence in health authorities	2.0	[2.0;3.0]	1.5	[1.0;2.0]
Confidence in general practitioner	3.0	[2.0;3.0]	2.0	[1.0;2.0]

Note

* Cronbach's coefficient alpha assessed internal scale reliability when multiple items measured a construct (perception of influenza vaccine benefits, perception of barriers to the influenza vaccination and cues to action). A value of >0.6 was considered indicative of acceptable internal scale reliability. All construct scores were analyzed as continuous scales.

a) Post-result questionnaire

Variables	Participants willing to be vaccinated (N = 216)		Participants not willing to be vaccinated (N=93)	
	N or Median	% or (Min ;Q1;Q3 ;Max)	N or Median	% or (Min ;Q1;Q3 ;Max)
<u>Perception of influenza severity</u>				
No or mildly severe disease	13	(6.0)	11	(12.5)
Moderate or highly severe disease	202	(94.0)	77	(87.5)

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Table 3-a: Factors associated with the willingness to be vaccinated against influenza in the subsequent season in the pre-virological result questionnaire; fully adjusted model, FLUVAC study 2012-2014 (N=299)

Variables	Adjusted* Relative Risk	95% CI	P- value
<u>Influenza vaccination status</u>			
Current season influenza vaccination status			
No vaccination	1	ref	
Vaccination	1.76	(1.49-2.07)	<0.001
<u>Attitudes towards influenza disease and vaccination</u>			
Perception of influenza severity			
No/mildly severe	1	ref	
Moderate or highly severe	1.01	(0.76-1.34)	0.94
Perception of vaccination			
Strongly against/against/don't know	1	ref	
Favorable/strongly favourable	1.04	(0.79-1.36)	0.78
Perception of influenza vaccine benefits	1.08	(1.04-1.13)	<0.001
Cues to action	1.06	(1.02-1.10)	0.007
Perception of barriers to the influenza vaccination	0.95	(0.92-0.98)	<0.001

CI: Confidence Interval

*Adjusted for season of inclusion, age, location of participating hospitals, sex and comorbidities

Table 3-b: Factors associated with the post-virological result willingness to be vaccinated against influenza in the subsequent season; fully adjusted model, FLUVAC study 2012-2014 (N=296)

Variables	Adjusted Relative Risk	95% CI	p-value
<u>Influenza vaccination status</u>			
Current season influenza vaccination status			
No vaccination	1	ref	<0.001
Vaccination	1.38	(1.20-1.59)	
<u>In-hospital clinical evolution</u>			
In-hospital complication			
No	1	ref	0.19
≥1	1.09	(0.96-1.23)	
Influenza laboratory test result			
Influenza negative	1	ref	0.02
Influenza positive	1.18	(1.03-1.34)	
<u>Attitudes towards influenza disease and vaccination</u>			
Perception of influenza severity			
No/mildly severe	1	ref	0.68
Moderate or highly severe	1.07	(0.76-1.51)	
Perception of vaccination			
Strongly against/against/don't know	1	ref	0.53
Favorable/strongly favourable	1.08	(0.85-1.37)	
Perception of influenza vaccine benefits	1.06	(1.02-1.10)	0.002
Cues to action	1.08	(1.03-1.12)	<0.001
Perception of barriers to the influenza vaccination	0.97	(0.94-0.99)	0.02

CI: Confidence Interval

**Adjusted for season of inclusion, age, location of participating hospitals, sex and comorbidities*