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Conflicts of Interest. All authors, none.

Keywords. COVID-19; vaccine; health care workers; vaccine hesitancy; influenza

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ABSTRACT

Objective. To characterize the willingness to get the third COVID-19 vaccine dose among health care workers (HCWs).

Methods. A cross-sectional study using a self-administered questionnaire proposed on a voluntary basis to all HCWs of a French teaching hospital in October and November 2021.

Results. Of 1,655 HCWs who completed the questionnaire, 64.2% were willing to receive the third dose, 20.1% were hesitant, and 15.7% were reluctant. On multivariate analysis, older age ($p<0.0001$), medical and executive staff, willingness to receive the flu vaccine (OR=5.72 [4.24-7.64]), previous vaccine scheme with ChAdOx1 nCoV-19 (AstraZeneca) (OR=2.13 [1.58-2.87]), and history of COVID-19 with a complete COVID-19 vaccine scheme (OR=2.77 [1.04-7.41]) were independent predictors of HCWs' willingness to get the third dose.

Conclusions. One third of HCWs were hesitant or opposed to a third COVID-19 vaccine dose. Better knowledge of determinants of the willingness to get this third dose may improve communication and vaccine strategy.

1. Introduction

Health care workers (HCWs) are at increased risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to their exposure to patients and to their household and community exposure [1]. Several vaccines have been developed with high effectiveness [2-4]. HCWs were among the priority target populations to protect them, their patients, and their relatives, and to avoid HCW absenteeism. In France vaccination of HCWs began in January 2021 on a voluntary basis. Since September 15, 2021, complete vaccination (two doses of vaccine) was made compulsory for all HCWs.

Unfortunately, breakthrough infections were reported in fully vaccinated HCWs as early as August 2021, irrespective of the vaccine scheme [5-6]. More recently, Yamamoto *et al.* reported COVID-19 breakthrough infections among fully vaccinated HCWs during the fifth wave, dominated by the delta variant [7]. At the same time, reduced vaccine effectiveness was reported as early as 3 months after the second vaccine dose in the general population [8-10] highlighting the need for a third dose, particularly in HCWs [11]. Several landmark papers confirmed the effectiveness of a third dose in various populations, with a dramatic impact on the COVID-19 incidence [12], but also on COVID-19 severity [13] and mortality [14]. However, acceptance of this initially unplanned third dose raised concerns in the overall context of vaccine hesitancy worldwide, particularly regarding COVID-19 vaccines [15-18]. Characteristics and determinants of the general population's and HCWs' willingness to get the third COVID-19 vaccine dose has not attracted much attention to date. We performed a cross sectional study to characterize the intention of HCWs towards this third vaccine dose, as well as their determinants.

2. Methods

The Rennes University Hospital is a 1,800-bed tertiary care center in Western France. Between October 25 and November 26, 2021 an anonymous self-administered questionnaire was proposed on a voluntary basis to all HCWs on the institutional internal website. We collected demographic characteristics, occupation, chronic medical conditions at risk for serious COVID-19 (obesity, cancer, diabetes, hypertension, immunodepression, etc.), COVID-19 history, and influenza vaccination status. The questionnaire included specific questions on previous COVID-19 vaccines (mRNA-BNT162b2 [Pfizer-BioNTech], mRNA-1273 [Moderna], ChAdOx1 nCoV-19 [AstraZeneca], and Ad26.COV2.S [Janssen], corresponding to COVID-19 vaccines available in France during the study period), as well as on the intention to receive a third dose as recommended for HCWs in France at that time. More precisely, HCWs were asked the following questions: 'What is your position regarding the third dose of COVID-19 vaccine?'. They could either check 'I am favorable', 'I am hesitant', or 'I am against it'. HCWs not eligible to a third dose at baseline (recent COVID-19 infection, contraindication) were excluded from analyses.

We first conducted a univariate analysis to describe the associations between the willingness to get the third COVID-19 vaccine dose (categorized as pro / hesitant / con) and HCW characteristics, flu vaccination status, COVID-19 history, and previous scheme of COVID-19 vaccination. All multivariate models were *a priori* systematically adjusted for age, gender, and occupation and then all variables associated with a *p* value <0.20 were computed by a stepwise multivariate analysis based on a logistic regression model, where the primary outcome was modelled in a binary approach: i) pro; ii) hesitant or con.

Results are presented as odds ratio (OR) with their 95% confidence intervals. A p value below 0.05 was considered significant. Statistical analyses were performed using the SAS® package, v9.4.

3. Results

Overall, 1,713 HCWs completed the questionnaire (participation rate: 21.5%). We excluded HCWs with no indication for a third dose: contraindication to all COVID-19 vaccines, recent COVID-19 infection (<3 months), or unknown COVID-19 vaccine status (n=58). Of the remaining 1,655 HCWs, 1,063 (64.2%) declared to be willing to receive the third dose of COVID-19 vaccine, while 333 (20.1%) were hesitant, and 259 (15.7%) were opposed to it (Table 1). In univariate analysis, older age ($p<0.0001$) and occupation – namely health executives and medical staff – ($p<0.0001$) were associated with the willingness to receive the third dose. Previous or current regular flu vaccination (Table 2) was also strongly associated with the willingness to receive the third dose of COVID-19 vaccine ($p<0.0001$). Interestingly, previous vaccination with at least one dose of ChAdOx1 nCoV-19 was also associated with the willingness to receive the third COVID-19 vaccine dose (OR 1.71 [1.35-2.17]), while the opposite was observed for HCWs previously vaccinated with at least one dose of mRNA-1273 (OR 0.66 [0.51-0.86]). Overall, a COVID-19 history was not associated with the intention to receive the third dose (OR 0.78 [0.51-1.20]). However, we observed two distinct profiles within HCWs with previous COVID-19 infection: those who had a complete vaccine scheme were more likely to be in favor of the third dose (OR 2.56 [1.06-6.23]), as compared to those with incomplete vaccine scheme (OR 0.45 [0.26-0.76]). In multivariate analysis (Table 3), in addition with an association with age and occupation, the willingness to receive the flu vaccine for the following season (OR 5.72 [4.24-7.64]), previous vaccine scheme with a least one dose of ChAdOx1 nCoV-19 (OR=2.13 [1.58-2.87]), and a history of COVID-19 associated with a

complete COVID-19 vaccine scheme (OR 2.77 [1.04-7.41]) were independently associated with the willingness to get the third dose of COVID-19 vaccine.

4. Discussion

We observed that the willingness to receive a third dose of COVID-19 vaccine in HCWs was associated with older age, flu vaccination status, and specific occupations (i.e. health executives and medical staff as compared to non-medical HCWs). Interestingly, on multivariate analysis we identified unexpected independent predictors of willingness to get the third dose: *i)* history of COVID-19 in HCWs with adequate vaccination scheme, and *ii)* previous vaccine scheme with a least one dose of ChAdOx1 nCoV-19. The association between older age and willingness to receive a COVID-19 vaccine was identified in most studies on COVID-19 vaccine hesitancy, for the first dose and in the general population as well [15-16]. This probably reflects individual motivation, as age is the most powerful predictor of poor outcome after COVID-19 especially in a population of workers with a relatively low frequency of other risk factors. Hence, the benefit/risk ratio of COVID-19 vaccine appears particularly obvious in older individuals. The association of the flu vaccination status and the willingness to receive the COVID-19 vaccine is also quite intuitive, as both are associated with similar characteristics, including trust in institutional vaccine recommendations and awareness that HCWs are at high risk of transmitting these viruses to patients and relatives [16].

The most surprising findings of our study are as follows. Firstly, previous administration of the ChAdOx1 nCoV-19 vaccine was independently associated with the willingness to get the third COVID-19 vaccine dose. This may be due to convincing data that the effectiveness of the ChAdOx1 nCoV-19 vaccine is sub-optimal for the prevention of the delta variant, largely dominant by the time of the study (October-November 2021) [18]. The dramatic emergence

of the Omicron variant in December 2021 in France probably reinforced this association. Hence, HCWs previously vaccinated with the ChAdOx1 nCoV-19 vaccine seems more likely to ask for a third dose to improve their immune response against the delta variant. Secondly, the heterogeneous association between history of COVID-19 and willingness to receive the third vaccine dose is less clear: previous COVID-19 infection in HCWs was associated with a higher or with a lower willingness to get the third dose depending on their COVID-19 vaccination scheme. We may hypothesize that past medical history of COVID-19 would reinforce the willingness to receive the third dose in order to avoid the previously experienced COVID-19 symptoms and to reinforce protection. However, the reason it would only apply to HCWs with a complete previous vaccine scheme remains unclear. Our data may suggest that HCWs with a COVID-19 history and a single dose of COVID-19 vaccine in a context of complete mandatory scheme represent a population less prone to the vaccine.

Our study has several limitations. First, as it was a monocentric study conducted over a short period of time, its findings may not be generalizable to other settings or other periods of the COVID-19 pandemics. These limitations are particularly relevant given the rapid evolution of the epidemiology, scientific knowledge, and HCWs' feelings about the COVID-19 pandemic and the optimal way to manage it [16]. Second, the recruitment of subjects on a voluntary basis implies that representability may not be guaranteed even if the general characteristics of respondents did not differ from those of the whole population (data not shown). Third, we only collected declarative data, and no control of answer accuracy was performed. However, this study has several strengths such as its large sample size (1,655 questionnaires evaluated), the anonymous collection of data, and the focus on an important issue which has thus far not been investigated (to our knowledge). Indeed, as it became obvious that a third dose of COVID-19 vaccine seemed necessary to boost the protection of

the population [11-13], including HCWs, better knowledge of determinants of the willingness to get this third dose may improve communication and vaccine strategy, particularly regarding HCWs as it is a key population in the fight against COVID-19.

In conclusion, we found that most eligible HCWs (64%) were willing to receive the third COVID-19 vaccine dose, while 20% were hesitant, and 16% were opposed to it. Older age, specific occupation categories, influenza vaccine status, and having received the ChAdOx1 nCoV-19 vaccine were associated with willingness to receive the third dose.

Authors' contribution

CP, AS, ET, RG, and PT participated in the study design. CP, ET, VT, RNV, and PT were involved in the implementation of the vaccine campaign and communication to health care workers. CP performed primary analyses and wrote the first draft of the article. RG and PT critically reviewed the first draft of the manuscript. All authors contributed to the final version of the manuscript.

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Table 1. Characteristics of health care workers according to their willingness to get the third COVID-19 vaccine dose (n=1,655)

Variables	Willingness to get the 3 rd COVID-19 vaccine dose			
	Pro	Hesitant	Con	Hesitant/Con vs Pro
	n (%)	n (%)	n (%)	
	1,063 (64.2)	333 (20.1)	259 (15.7%)	
			p value¹	OR 95%CI²
Gender			0.68	
Female	811 (63.7)	259 (20.3)	204 (16.0)	1.00
Male	254 (66.0)	75 (19.5)	56 (14.6)	1.10 [0.87-1.40]
Age (years)			<0.0001	
<30	165 (55.6)	60 (20.2)	72 (24.2)	1.00
30-39	270 (59.9)	99 (22.0)	82 (18.2)	1.19 [0.89-1.61]
40-49	319 (64.7)	105 (21.3)	69 (14.0)	1.47 [1.09-1.97]
50+	309 (74.6)	69 (16.7)	36 (8.7)	2.35 [1.71-3.24]
Occupation			<0.0001	
Administrative staff	146 (57.3)	45 (17.7)	64 (25.1)	0.84 [0.62-1.14]
Cleaners, Auxiliary-nurses, Stretcher-bearers	90 (51.4)	35 (20.0)	50 (28.6)	0.66 [0.47-0.94]
Health Executives	59 (85.5)	7 (10.1)	3 (4.4)	3.68 [1.84-7.37]
Nurses / Other care staff	306 (61.6)	129 (26.0)	62 (12.5)	1.00
Medical staff, residents, students	260 (85.8)	31 (10.2)	12 (4.0)	3.77 [2.60-5.46]
Pharmacy / Laboratory staff	29 (48.3)	16 (26.7)	15 (25.0)	0.58 [0.34-1.00]
Workers, technicians	52 (52.0)	23 (23.0)	25 (25.0)	0.68 [0.44-1.04]

Support staff	48 (61.6)	20 (25.6)	10 (12.8)	1.00 [0.61-1.63]
Other staff members	75 (61.5)	28 (23.0)	19 (15.6)	1.00 [0.66-1.50]
Comorbidities (at least one)³			0.31	
No	1,005 (63.8)	322 (20.4)	248 (15.8)	1.00
Yes	60 (71.4)	12 (14.3)	12 (14.3)	1.42 [0.87-2.30]

¹: *p* value, Chi² test

²: *p* value, logistic model, univariate analysis

³: hypertension, obesity, chronic respiratory conditions, cancer, immunosuppression

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Table 2. Flu and COVID-19 vaccination status according to the willingness to get the third COVID-19 vaccine dose

Variables	Willingness to get the 3 rd COVID-19 vaccine dose			
	Pro	Hesitant	Con	Hesitant/Con vs Pro OR [95%CI]
Flu vaccine status				
Previous flu vaccines				
Never	196 (43.7)	105 (23.4)	148 (32.9)	1.00
Never, except for last winter	169 (54.7)	84 (27.2)	56 (18.1)	1.56 [1.17-2.09]
Regularly	698 (77.8)	144 (16.0)	55 (6.1)	4.55 [3.57-5.81]
Flu vaccine intention (2021-2022)				
Con	134 (35.3)	89 (23.4)	157 (41.3)	1.00
Hesitant	103 (43.6)	80 (33.9)	53 (22.5)	1.43 [1.02-1.99]
Pro	826 (79.5)	164 (15.8)	49 (4.7)	7.13 [5.50-9.24]
Covid-19 history				
No	1,009 (64.6)	314 (20.1)	240 (15.4)	1.00
Yes	54 (58.7)	19 (20.7)	19 (20.7)	0.78 [0.51-1.20]
COVID-19 history and vaccinal scheme				
Complete scheme without COVID-19 history	1,009 (64.6)	314 (20.1)	240 (15.4)	1.00
Complete scheme with COVID-19 history	28 (82.4)	4 (11.8)	2 (5.8)	2.56 [1.06-6.23]
Incomplete scheme with COVID-19 history	26 (44.6)	15 (25.9)	17 (29.3)	0.45 [0.26-0.76]
Type of COVID-19 vaccine (first dose)				
mRNA-BNT162b2	403 (62.5)	124 (19.2)	118 (18.3)	1.00

mRNA-1273	179 (52.3)	92 (26.9)	71 (20.8)	0.66 [0.51-0.86]
ChAdOx1 nCoV-19	461 (74.0)	106 (17.0)	56 (9.0)	1.71 [1.35-2.17]
Incomplete scheme ²	20 (44.4)	11 (24.4)	14 (31.1)	0.48 [0.26-0.88]
ChAdOx1 nCoV-19 (at least one dose)				<0.0001
Yes	582 (59.0)	216 (21.9)	189 (19.6)	1.98 [1.59-2.47]
No	461 (74.0)	106 (17.0)	56 (9.0)	1.00
Incomplete scheme ²	20 (44.4)	11 (24.4)	14 (31.1)	0.56 [0.31-1.02]

¹: *p* value, logistic model, univariate analysis

²: subjects with an incomplete vaccine scheme (no information on some doses) and COVID-19 history

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Table 3. Determinants of the willingness to get the third COVID-19 vaccine dose (multivariate model, n=1,597)

Variables	OR	95%CI ¹	p value
Gender			0.15
Female	1.00		
Male	0.80	[0.59-1.08]	
Age (years)			<0.0001
<30	1.00		
30-39	1.04	[0.73-1.47]	
40-49	1.48	[1.05-2.10]	
50-+	3.08	[2.09-4.53]	
Occupation			<0.0001
Administrative staff	1.27	[0.89-1.81]	
Cleaners, Auxiliary-nurses, Stretcher-bearers	1.00	[0.67-1.48]	
Health Executives	3.04	[1.44-6.41]	
Nurses / Other care staff	1.00		
Medical staff, residents, students	3.33	[2.19-5.05]	
Pharmacy / Laboratory staff	0.72	[0.39-1.32]	
Workers, technicians	1.49	[0.87-2.42]	
Support staff	1.10	[0.63-1.94]	

Other staff members	1.31	[0.82- 2.08]
Comorbidity (at least one)²		0.14
No	1.00	
Yes	1.52	[0.87- 2.63]
Flu vaccine intention (2021-2022 season)		< 0.0001
Con	1.00	
Hesitant	1.31	[0.92- 1.87]
Pro	5.72	[4.24- 7.64]
COVID-19 history and vaccinal scheme		0.12
Complete scheme without COVID-19 history	1.00	
Complete scheme with COVID-19 history	2.77	[1.04- 7.41]
Incomplete scheme with COVID-19 history	1.07	[0.32- 3.52]
Type of first vaccine dose		<0.0001
mRNA-BNT162b2	1.00	
mRNA-1273	1.02	[0.74- 1.41]
ChAdOx1 nCoV-19	2.13	[1.58- 2.87]

¹: *p* value, multivariate analysis, logistic regression model,

²: hypertension, obesity, chronic respiratory conditions, cancer, immunosuppression

et 2021; **397**(10293): 2461-2.

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