ORIGINAL RESEARCH ARTICLE

Impact of Vaccine Hesitancy on Onset, Severity and Type of Self-reported Adverse Events: A French Cross-Sectional Survey

Charles Khouri[1,2] · Ayoub Larabi[1] · Pierre Verger[3,4,5] · Fatima Gauna[4] · Jean-Luc Cracowski[1,2] · Jeremy Ward[3,6]

Abstract

Introduction Little is known about the impact of mandatory vaccination on people who are reluctant to be vaccinated, despite the potential importance in terms of public health policy.

Objective We aimed to explore the relationship between vaccine hesitancy and onset, severity and characteristics of self-reported adverse events.

Methods We used a cross-sectional online survey conducted in 2021 among a representative sample of the French population aged 18 years and older ($n = 1593$). All reported adverse events were analyzed and categorized by trained experts in drug safety and pharmacovigilance. Multivariate binomial regressions on the onset of self-reported adverse events, vaccine hesitancy categories and predefined responders' characteristics were performed.

Results Overall, 590 (37.0%) participants reported at least one adverse event, with 121 (20.5%) considered it to be severe. Proportions of reported adverse events, ranging from 18% (in non-reluctant responders) to 65% (in very reluctant responders), and their severity, ranging from 5% (non-reluctant responders) to 41% (very reluctant responders), depended highly on attitudes toward vaccination. The adverse events profile remained similar between groups. In the multivariate regression model, beyond attitude toward vaccination, younger age and female gender were significantly associated with higher reporting of vaccine adverse events.

Conclusions Our results suggest that vaccine hesitancy could be a major driver of patient-reported vaccine-related adverse events and their perceived severity. In this context, vaccinators must pay special attention to reluctant patients and inform them on the possible nocebo nature of these adverse events so as to prevent them.

Key Points

Vaccine hesitancy is associated with a large increase of self-reported adverse events and their perceived severity.

A significant proportion of adverse events reported by the people reluctant to be vaccinated are nocebo effects.

Caregivers must pay particular attention to vaccination-reluctant individuals and inform them of the nature of potential adverse reactions to prevent nocebo effects.

J. L. Cracowski and Jeremy Ward contributed equally to this work.

✉ Charles Khouri
  CKhouri@chu-grenoble.fr

1 Pharmacovigilance Unit, Grenoble Alpes University Hospital, Grenoble, France

2 HP2 Laboratory, Inserm U1300, Grenoble Alpes University, Grenoble, France

3 VITROME (Aix Marseille Université, IRD, AP-HM, SSA), Marseille, France

4 Observatoire régional de la santé PACA (ORS Paca), Aix-Marseille Université, Marseille, France

5 Inserm, F-CRIN, I-REIVAC/COVIREIVAC, Paris, France

6 CERMES3 (INSERM, CNRS, EHESS, Université de Paris), Villejuif, France

1 Introduction

In 2021, confronted with plateauing vaccination coverage against Covid-19 and vaccine hesitancy, public health decision makers in many countries considered coercive measures such as health passports or mandates [1, 2]. On 12 July 2021, the French president announced the implementation of a health passport requiring people to present proof of vaccination or a negative test to participate in many day-to-day activities ranging from going to the pub to accompanying a relative to the hospital. This policy dramatically improved vaccination rates from 39% in June 2021 to 75% in October 2021 [3], but it also caused many of those who had doubts or were anxious about the vaccines to feet coerced into being vaccinated [4, 5]. Worrisome expectations and social contexts (e.g., knowing someone who reported side effects) are well-known determinants of nocebo effects and symptom misattribution [6, 7]. Adverse events have been reported with many drugs or vaccines, such as in France after the change in the formulation of Levothyrox and the reports of incipient functional neurological disorders with Covid-19 vaccines [8, 9]. Beyond these stereotypical examples, the impact of mandatory vaccination on people who are reluctant to be vaccinated is still unknown despite its potential importance in terms of public health policy. We therefore drew on the recent French experience with the Covid-19 Health pass to collect data on the relationship between attitudes towards vaccination and the onset, severity and characteristics of self-reported adverse events.

2 Methods

We used a cross-sectional online survey conducted in 2021 between 22 September and 1 October among a representative sample of the French adult population (aged >18 y) ($n = 2015$) [10].

Participants were randomly selected from an existing online research panel of >750,000 households (Bilendi SA$^{®}$) and contacted by email. We then applied a quota sampling method to achieve a representative sample of 2015 respondents from the French adult population in terms of age, gender, occupation and population in the area of residence [11]. In total, 51,400 invitations were sent to reach this sample (response rate 3.9%). This survey included 106 questions, 10 of which were deemed relevant to our research and pre-specified in a protocol prior access to the data. Details and wording of the selected questions are provided in Supplementary Table 1 (see electronic supplementary material [ESM]).

In addition to background socioeconomic variables (age, gender, educational and economic level) and sources of information (television, radio, print media, internet media sites, other websites or social networks), we asked respondents whether they had been vaccinated against Covid-19, when and whether they had any doubts or reluctance about the vaccine they received. The following answers were proposed: "very", "a little", "not really", "not at all", "I don't know" or "I don't wish to answer". To test the relationship between vaccine hesitancy (i.e., the reluctance to get vaccinated because of concerns and doubts about the vaccines or vaccination in general) and the self-reporting of side effects, we asked if they had experienced any adverse events and if so, whether they classified the adverse event(s) as "severe", that is, it had "consequences on their personal or professional daily life". We also asked them to describe these adverse events.

All adverse events were then analyzed and categorized by trained experts in drug safety and pharmacovigilance (CK, JLC, AL). Adverse event categories were defined based on the 100 first responses and collectively discussed to reflect our prior knowledge on Covid-19 vaccines safety and MedDRA classification [12]. The remaining responses were independently categorized by two reviewers (CK and AL) and discrepancies were resolved through discussion among the team. The proportion and severity of adverse events between responders with no reluctance and those very reluctant were compared using chi-squared tests with a p value <0.003 deemed significant (Bonferroni correction used given the number of adverse event categories tested). Lastly, we performed multivariate binomial regressions on vaccine hesitancy categories and predefined responders' characteristics (age, sex, sources of information, educational level and economic status) to explore any link with the self-reporting of adverse events (dependent variable).

Statistical analyses were performed with R (version 4.1.1) and Jamovi. This study was approved by the INSERM Review Board (IRB 00003888; approval number 21-770) and the protocol was pre-registered on Open Science Framework (https://osf.io/5wejg).

3 Results

Among the 2015 respondents, 1593 had been vaccinated, answered questions about their doubts or reluctance about the vaccine they got, and were included in the analysis. Of these, 203 (12.7%) were very reluctant, 481 (30.2%) a little reluctant, 399 (25.0%) not really reluctant and 510 (32.0%) not reluctant at all (23 participants did not know and 9 did not wish to answer) at the time of vaccination. Compared with responders with no reluctance at all, very reluctant

responders were more likely to be young (median age 45 vs 62 years), female (67% vs 43.5%), have lower income (40% vs 27% <2000 euros per month), lower educational level (43% vs 33% of undergraduate respondents) and get informed on social networks (16% vs 8% using social networks) (Table 1).

Overall, 590 (37.0%) participants reported at least one adverse event, among whom 121 (20.5%) considered it to be severe. The mean number of reported adverse events ranged from 1.7 for responders with no reluctance at all to 2.2 for very reluctant responders. When examining changes over time in responders' attitudes toward vaccination we found that the proportion of reluctantly vaccinated people increased during 2021 and became the majority after the government's announcement of the health pass requirement in France on 12 July (Fig. 1). Thematic analysis of the responses yielded the definition of 11 types of adverse events: injection-site pain, fatigue, pyrexia, headache, musculo-skeletal disorders, gastro-intestinal disorders, menstrual disorders, hypersensitivity reactions, dizziness, cardio-vascular disorders and respiratory disorders by decreasing incidence. The proportions of reported adverse events ranged from 18% (not reluctant at all responders) to 65% (very reluctant responders), and if severe ranged from 5% (not reluctant at all responders)

to 41% (very reluctant responders), and depended highly on the responders' attitudes toward vaccination (Table 2). The distribution of these adverse events according to attitudes toward Covid-19 vaccination are presented in Fig. 2A and whether severe or not, in Fig. 2B. The proportions of each type of adverse event were similar between groups, except for a larger proportion of gastrointestinal disorders in the very reluctant group compared with the group with no reluctance at all to get vaccinated ($p < 0.003$). However, the perceived severity of these adverse events strongly differed between groups, with a higher proportion of severe events in responders who were very reluctant to get vaccinated, notably for injection-site pain, pyrexia, headache and fatigue ($p < 0.003$). In the multivariate binomial regression model beyond the attitude toward vaccination, younger age and female gender were significantly associated with the higher reporting of a vaccination-related adverse event (Table 3).

4 Discussion

To our knowledge, this is the first study assessing the relationship between vaccine hesitancy against Covid-19 vaccination and the onset, type and perceived severity

Table 1 Characteristics of vaccinated responders according to attitude toward COVID-19 vaccines

Responders' characteristics	Not at all reluctant (n = 510)	Not really reluctant (n = 399)	A little reluctant (n = 481)	Very reluctant (n = 203)
Age [y], median (IQR)	62 (28)	60 (33)	51 (28)	45 (24)
18–34 y	68 (13%)	72 (18%)	116 (24%)	63 (31%)
35–64 y	226 (44%)	176 (44%)	256 (53%)	112 (55%)
65+ y	216 (42%)	151 (38%)	109 (23%)	28 (14%)
Sex (M/F)	288/222	189/210	216/265	67/136
Income (euros/month)				
< 2000	136 (27%)	104 (26%)	164 (34%)	81 (40%)
2000–4000	225 (44%)	179 (45%)	206 (43%)	75 (37%)
>4000	95 (19%)	70 (18%)	60 (12%)	12 (6%)
NR	54 (11%)	46 (12%)	51 (11%)	35 (17%)
Educational attainment				
< Bac	169 (33%)	143 (36%)	180 (37%)	87 (43%)
Bac to Bac +2 y	193 (38%)	146 (37%)	193 (40%)	72 (35%)
Bac +3 or more	148 (29%)	110 (28%)	108 (22%)	44 (22%)
Main information medium				
Television	60 (12%)	43 (11%)	65 (14%)	24 (12%)
Radio	78 (15%)	48 (12%)	56 (12%)	25 (12%)
Print media	82 (16%)	69 (17%)	83 (17%)	35 (17%)
Internet media sites	56 (11%)	51 (13%)	47 (10%)	25 (12%)
Other websites	63 (12%)	43 (11%)	59 (12%)	16 (8%)
Social networks	43 (8%)	46 (12%)	64 (13%)	33 (16%)
NR	128 (25%)	99 (25%)	107 (22%)	45 (22%)

Bac (Baccalauréat) = high school graduation, *NR* no response
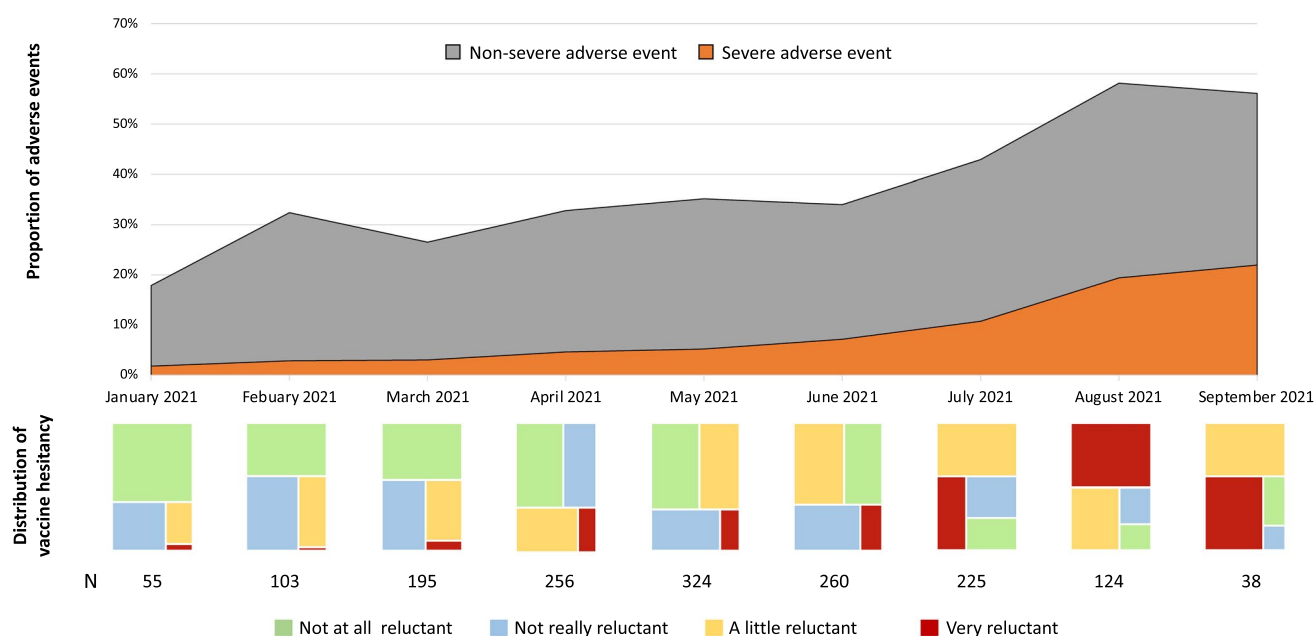
Fig. 1 Time trend evolution of the proportion of responders reporting adverse events according to their attitudes toward COVID-19 vaccines. Data from a cross-sectional online survey among a representative sample of the French population

Table 2 Proportion of adverse events and severe adverse events reported by online survey participants according to attitudes toward COVID-19 vaccines

Attitudes toward COVID-19 vaccines	Number of responders	Proportion of adverse events reported by responders (%)	Proportion of adverse events reported as 'severe' by responders (%)
Not at all reluctant	510	18	5
Not really reluctant	399	33	11
A little reluctant	481	45	21
Very reluctant	203	65	41

of patient-reported vaccine-related adverse events. Our results suggest that vaccine hesitancy strongly influences the reporting of perceived adverse events and their impact on daily activities. Two main hypotheses can be drawn from these results: an impact of vaccine hesitancy on the willingness to report adverse events and a higher incidence of nocebo effects in the population reluctant to be vaccinated. Nocebo effects are the consequences of patients' negative expectations about drugs that could be induced by other peoples' suggestions, negative stories in the media, the way a drug or vaccine is presented or prior therapeutic and learning experiences [6, 7, 13]. Pain neuromodulators such as cholecystokinin and the cerebral region implicated in anxiety have been associated with nocebo hyperalgesia [14, 15]. Moreover, two series multiple crossover (N-of-1) trials have demonstrated that beyond genuine nocebo effects, symptom misattribution constitutes a non-negligeable proportion of adverse events associated with statin use [7, 16]. These results are in line with a meta-analysis of Covid-19 vaccine randomized controlled trials which

found that 76.0% of systemic adverse events and 24.3% of local adverse events could be attributed to nocebo responses after the first vaccination, without differences in the types of adverse events reported in the placebo and vaccine arms [17]. In this meta-analysis, the proportion of adverse events reported in the vaccine arms after the first and second doses were 46.3% and 61.4% for systemic adverse events and 66.7% and 72.8% for local adverse events, respectively. In our online survey, only 37.0% of responders reported experiencing an adverse event; this difference could likely be attributed to the retrospective solicitation to report adverse events. Moreover, the multivariate regression analysis showed that beyond vaccine hesitancy, young female adults are more prompt to report adverse events. These characteristics are also well known factors associated with adverse event self-reporting in pharmacovigilance databases and could be related in our study to higher anxiety and negative expectations in this population [18, 19]. While educational level and income have been associated with vaccine hesitancy, they were
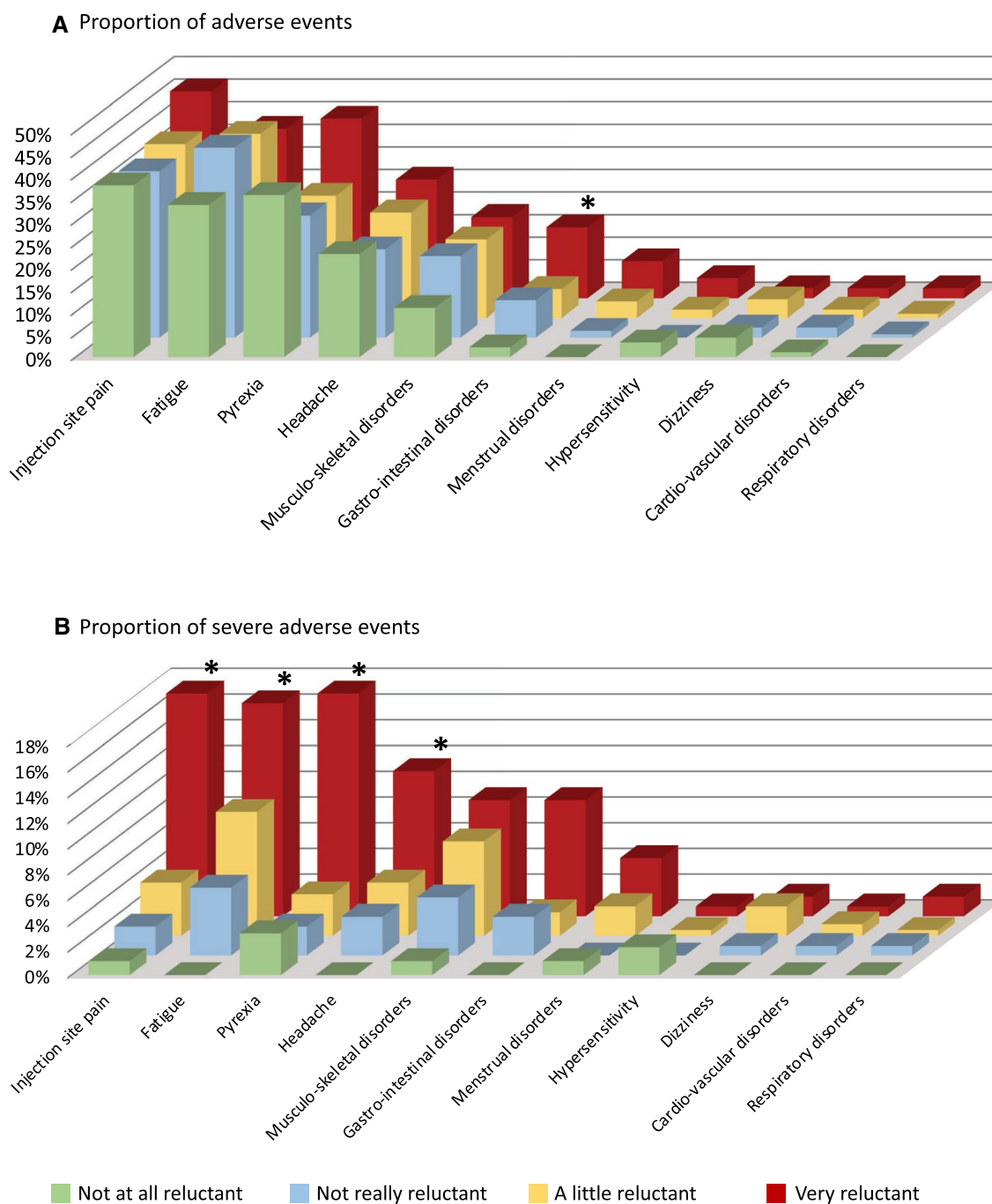
A Proportion of adverse events

B Proportion of severe adverse events

Not at all reluctant   Not really reluctant   A little reluctant   Very reluctant

Fig. 2 Distribution of reported adverse events and severe adverse events according to their attitudes toward COVID-19 vaccines from a cross-sectional online survey among a representative sample of the French population. *Significant differences between responders with no reluctance and a lot of reluctance to get vaccinated (chi-squared, $p < 0.003$)

not independent determinants of adverse event reporting in our study [20].

Although the reasons for vaccine hesitancy are diverse and complex, its main identified drivers are doubt about the safety of vaccines and complacency (low risk perceptions of Covid-19 for personal health and subsequently low expected benefit of vaccines) [4, 20]. When people have vaccination

imposed on them, these doubts about the benefit–risk balance of vaccines may translate into a high sensitivity to perceive adverse reactions. Indeed, nocebo effects have been associated with several factors which are amplified in the current Covid-19 pandemic and vaccination campaign. Conflicting information on the efficacy of different vaccines, the rapid development of these vaccines, the government

Table 3 Results of the multivariate binomial regression model

Responders' characteristics	Odds ratio (95% CI)	p value
Main information medium (ref print media)		
Other websites	0.66 (0.36–1.21)	0.18
Radio	0.82 (0.51–1.33)	0.43
Television	1.00 (0.65–1.53)	0.99
Social networks	1.04 (0.52–2.10)	0.92
Internet media sites	1.00 (0.60–1.68)	0.99
Age (years)	0.99 (0.98–0.99)	**< 0.001**
Vaccine hesitancy (ref not at all reluctant)		
Not really reluctant	2.25 (1.61–3.14)	**< 0.001**
A little reluctant	3.38 (2.47–4.64)	**< 0.001**
Very reluctant	6.89 (4.54–10.44)	**< 0.001**
Income (ref <2000 euros/month)		
2000–4000 euros per month	1.08 (0.83–1.41)	0.56
>4000 euros per month	1.01 (0.69–1.47)	0.96
Educational level (ref <Bac)		
Bac to Bac +2 y	1.09 (0.83–1.44)	0.52
Bac +3y or more	1.09 (0.79–1.51)	0.59
Gender (ref male)		
Female	1.50 (1.19–1.91)	**< 0.001**

Bolded p values indicate significance

Bac Baccalauréat = high school graduation

pressure to get vaccinated, the negative reports in the media and the psychological distress due to the pandemic may largely increase anxiety and negative expectation of vaccines in sensitive members of the population [21]. Thus, the greater perceived impact of relatively innocuous adverse events in reluctant individuals could be an expression of doubts or anxiety about vaccination, a reaction to vaccination being imposed and more generally a means of protest against the government [4, 22].

This excess of adverse events may have several personal and public health consequences. The perception of an adverse event after a vaccination may reinforce personal negative expectation and worries about vaccine safety and subsequently result in the refusal of further vaccination and, in turn, increase the probability of experiencing further nocebo effects [23]. From a public health perspective, these adverse events may have non-negligeable impacts on absenteeism and saturate pharmacovigilance systems, impairing the detection of more serious adverse events due to other drugs by diluting safety signals [24].

Taken together, these results suggest that we could reduce the burden of vaccine-related adverse events by focusing on the negative expectations of vaccination-reluctant people. For example, several studies have provided evidence that informing people about nocebo responses and stressing the low probability of not experiencing adverse events can reduce nocebo effects [25–27]. Moreover, coupling information about possible adverse effects with information about the benefits of vaccination against Covid-19 may have some value [28, 29]. Lastly, discussing the patient's expectations and their prior experience of vaccination with them; as well as informing the public about the potential for nocebo responses might help reduce worries about Covid-19 vaccination and decrease vaccine hesitancy [20].

The main limitation of our results are their observational and retrospective nature. Indeed, patient reporting of adverse effects might be subject to recall bias and confounded by differences in responders' characteristics and the vaccines used between groups. Moreover, the study's cross-sectional design prevented us from interpreting the relationships found in this study in a causal way; indeed, we cannot exclude the possibility that vaccinated individuals who experienced adverse events may retrospectively indicate that they actually had been more reluctant to get vaccinated. Lastly, these results may not be generalizable to countries other than France, and we encourage researchers to conduct studies on this topic in other countries.

5 Conclusion

Our results suggest that vaccine hesitancy could be a major driver of patient-reported vaccination-related adverse events and their perceived severity, especially in a context where some people may feel coerced into being vaccinated. Whether authorities decide to resort to coercive measures or

not, it is crucial that greater efforts be devoted to persuading the public that vaccination is in the interest of both the individual and society as a whole. Covid-19 vaccination is likely to be a recurring endeavor. In this context, health professionals must not only vaccinate but also pay special attention to reluctant patients and specifically inform them on the nature of adverse reactions so as to prevent nocebo effects.

Declarations

Conflict of interest Authors declare that they have no competing interests.

Ethics approval This study was approved by the INSERM Review Board (IRB 00003888; approval number 21-770).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

Availability of data and material Data supporting this study are available on Open Science Framework (https://osf.io/5wejg).

Code availability Codes supporting this study are available upon reasonable request from the corresponding author (ckhouri@chu-grenoble.fr).

Author contributions Conceptualization: JW, JLC, CK; methodology: JW, JLC, CK; investigation: CK, AL, FG; visualization: CK; funding acquisition: JW, PV; supervision: JLC, JW, PV; writing—original draft: CK; writing—review and editing: CK, JLC, JW, FG, PV

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