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Short communication

Patients with history of covid-19 had more side effects after the first dose of covid-19 vaccine

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ABSTRACT

Introduction: COVID-19 vaccination seems to be the most pertinent pharmacologic public health measure to control the pandemic. Reactogenicity symptoms were frequent in vaccine recipients mostly mild to moderate and commonly reported after the second dose. However, there is a lack of data in patients with a previous diagnosis of Covid-19.
Methods: We analysed side effects of 311 patients after the first dose of Pfizer-BioNTech COVID-19 vaccine, in a french university hospital. We compared patients with COVID-19 history to naive individuals. All the data collected are based on self-reported, including COVID-19 exposure status.
Results: Overall, 229 (74%) patients reported at least one side effect. Among participants with history of Covid-19, 95% reported at least one adverse event versus 70% in naive patients ($p < 0.01$). However, symptom intensity was not different between the 2 groups.
Conclusion: Vaccine recipients with prior COVID-19 reported more, but no more serious, side effects than naive participants.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic continues to affect thousands people in France and is responsible, to date, for nearly 85 000 deaths. Currently, only corticosteroid and tocilizumab have so far proved to be effective in patients with severe forms of COVID-19, and vaccination seems to be the most pertinent pharmacologic public health measure to control the pandemic. The national COVID-19 vaccination program began in France at the end December 2020. Pfizer-BioNTech, an ARN vaccine, was the first recommended in France for over-50-years-old-healthcare-workers, or with high risk of severe COVID-19 and for patients over 75 years of age [1]. In phase 1/2/3 of the studies conducted by Pfizer-BioNTech, in vaccine recipients, reactogenicity symptoms were frequent, mostly mild to moderate, commonly reported after the second dose [2–4]. However, patients with a previous clinical or microbiologic diagnosis of Covid-19 were excluded.

We assessed the side effects after the first dose of Pfizer-BioNTech vaccine, comparing patients with or without history of COVID-19.

2. Method

We conducted a prospective and observational, single center study in university tertiary care hospital in Besançon, France. Eligible subjects were healthcare workers vaccinated with one dose of Pfizer-BioNTech COVID-19 vaccine. From 27 January to 5 February 2021, an anonymous questionnaire was proposed on site to each participant just before the second dose of vaccine (between 21 and 28 days after the first one). Data collected were subject's demographic characteristics, the occurrence and intensity of local (redness or pain at the injection site) and/or systemic symptoms (fatigue, vomiting, diarrhoea, headache, chills, fever, muscle pain, joint pain ...), and characteristics and data of prior COVID-19 disease. All the data collected in the questionnaire are based on self-reported, including COVID-19 exposure status. Our questionnaire was developed on the basis of the FDA Center for Biologics Evaluation and Research (CBER) guidelines on the toxicity classification scale for healthy adults.

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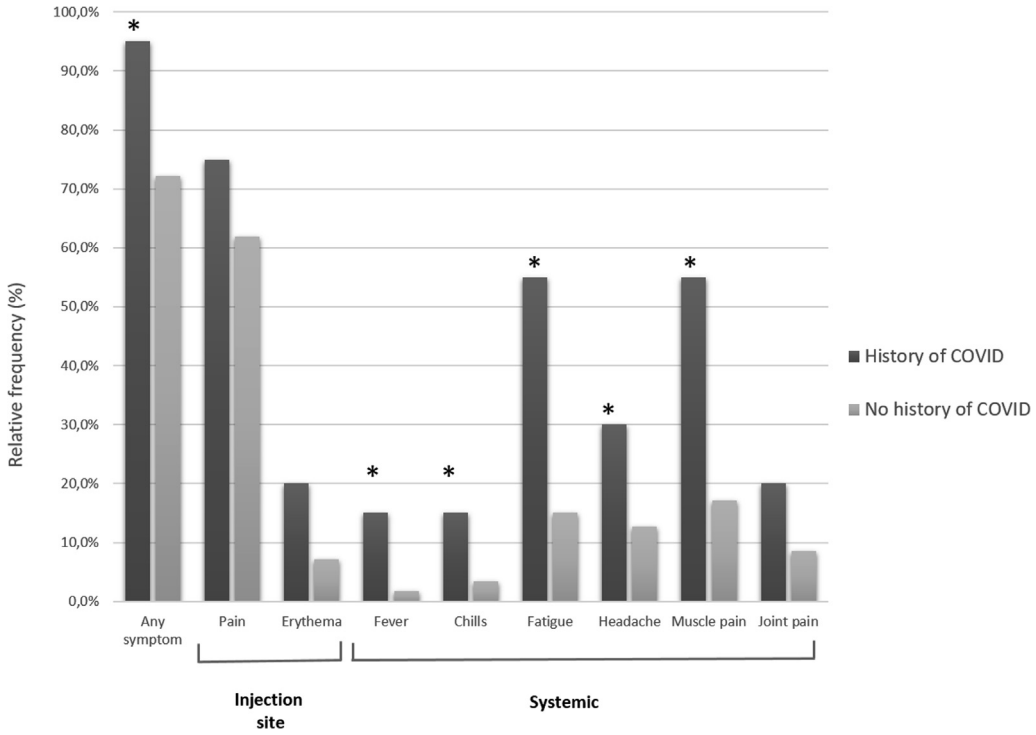

Fig. 1. Vaccine associated side effects experienced after the first dose of vaccine (N = 311 individuals). The local side effects occur with comparable frequency while the systemic symptoms are significantly more common in the individuals with history of COVID-19.

Comparisons of reactogenicity symptoms frequency between naive individuals, defined as asymptomatic, COVID-antibody status unknown and participants with history of COVID-19 were performed. All variables were examined by univariate analysis using the chi-square or Fisher's exact test, as appropriate. A p-value < 0.05 was considered significant.

Ethics approval and consent to participate: According to French legislation in this period, and because no intervention was performed on patients, no written informed consent was given by the patients Our study protocol followed the ethical guidelines of the declaration of Helsinki and was approved by our institutional review board.

3. Results

The questionnaire was completed by 311 of 351 healthcare workers vaccinated during the study period (response rate, 89%). The mean age was 55.4 ± 6.4 years and participants were mostly women (60%). History of COVID-19 was reported in 20 participants (6.4%). Among them, 19 had symptomatic COVID-19 confirmed by naso-pharyngeal RT-PCR, and only one had positive serology without symptoms. None of them were hospitalised. The mean duration between COVID-19 and first dose of vaccine was 10. 3 ± 2 months. Twelve of 20 (60%) participants did SARS-CoV2 serology and 8 were positive in a mean time of 8 ± 1 months before the vaccination. A total of 229 participants (74%) reported at least one side effect. Of the adverse reactions, 37% of participants reported systemic reaction (mainly fatigue (18%), headache (14%) muscle pain (20%)), and 66% reported a local event, such as pain at the site injection (63%) or erythema (8%). No side effects required additional medical attention.

Among participants with prior SARS-Cov-2 infection, 19/20 (95%) reported at least one adverse event, 18 (90%) at least one local reaction and 13 participants (65%) systemic side effects. Five participants had to lie down for 24–48 h, and only one was granted sick leave.

There was a relationship between history of COVID-19 and reactogenicity symptoms frequency. Vaccine recipients with prior COVID 19 infection experienced systemic side effects with a significantly higher frequency than naive patients (Fig. 1). However, symptom intensity was not different between the 2 groups, excepted for headache (Table 1).

4. Discussion

We herein report a comparative study of post-vaccination adverse events between vaccine recipients with a COVID 19 pre-existing immunity and naive individuals.

Reactogenicity is a part of the safety profile evaluation of a given vaccine. It refers to the potential for expected and unexpected local or systemic adverse reactions after vaccine administration. Overall, reactogenicity events after a first dose of Pfizer-BioNTech COVID-19 vaccine were common as previously described in pharmaceutical studies conducted by Pfizer-BioNTech [3–5]. Among all studied vaccine recipients, 84.7% reported at least one local injection site event and 77.4% at least one systemic reaction [3]. Pain at the injection site, fatigue, headache and muscle pain were the most common adverse events in these studies [2–4]. Symptoms usually peak by day 2 after vaccination and resolve by day 7 [4]. In our study, the rate of reported adverse events was lower than those in the safety studies. This is probably related to the fact that this is a real-world study, patients are warned in advance of vaccine side effects, and that they are self-reported and unsolicited.

Our study showed that vaccine recipients with a COVID 19 pre-existing immunity experienced significantly more frequent reactogenicity symptoms after the first vaccine dose compared to naive individuals, especially systemic symptoms. In the Pfizer-BioNTech Phase 3 study, 1125/37586 (3%) patients had a positive serology for SARS-CoV2. Of these, 545 patients were in the vaccine group and 580 in the placebo one. Adverse events reported were no more frequent in seropositive individuals [6].

Table 1
Characteristics of patients, frequency and intensity of side effects after the first dose of vaccine.

Characteristics	No history of COVID (n = 291)	History of COVID (n = 20)	P value
Age, median [Q25-75]	58.2 [53.6–61.0]	55.7 [52.3–59.3]	0.36
Sex M/F	113/175	10/10	0.34
No symptoms, n (%)	81 (28)	1 (5)	0.025
Injection site symptoms	186 (64)	18 (90)	0.018
Pain	180 (62)	15 (75)	0.24
Mild	105 (58)	6 (40)	0.1
Moderate	69 (38)	7 (47)	
Severe	6 (3.3)	2 (13)	
Erythema	21 (7.2)	4 (20)	0.065
Mild	13 (62)	1 (25)	0.29
Moderate	8 (38)	3 (75)	
Severe	0	0	
Systemic symptoms	101 (35)	13 (65)	<0.01
Fever	5 (1.7)	3 (15)	0.01
Mild (38–38.4°c)	5 (100)	2 (66)	0.9
Moderate (38.5–38.9°c)	0	1 (33)	
Severe (>39°c)	0	0	
Chills	10 (3.4)	3 (15)	0.043
Mild	9 (90)	1 (33)	0.5
Moderate	1 (10)	1 (33)	
Severe	0	1 (33)	
Fatigue	44 (15)	11 (55)	<0.001
Mild	22 (50)	6 (55)	0.82
Moderate	14 (32)	4 (36)	
Severe	8 (18)	1 (9.1)	
Headache	37 (13)	6 (30)	0.042
Mild	25 (68)	2 (33)	0.042
Moderate	9 (24)	1 (17)	
Severe	3 (8.1)	3 (50)	
Muscle pain	50 (17)	11 (55)	<0.001
Mild	34 (68)	6 (55)	0.48
Moderate	9 (18)	2 (18)	
Severe	7 (14)	3 (27)	
Joint pain	25 (8.6)	4 (20)	0.1
Mild	18 (72)	1 (25)	0.11
Moderate	4 (16)	1 (25)	
Severe	3 (12)	2 (50)	

In the last safety report of February 2021, the French National Agency for the Safety of Medicines and Health Products reported 239 cases of adverse reactions in people with a history of COVID-19 infection after the Pfizer-BioNTech vaccine [7]. The cases reported did not appear to present any specific characteristics in terms of the reported reactions severity, particularly reactogenicity. The proportion of patients who developed systemic reactogenic effects seemed higher in case of a history of COVID-19 (63.2% vs 50.8%), but with a lower severity. In contrast, in the current analyse, we did not report significant differences in severities, except for headache. This can be explained by the small sample size.

In immunogenicity trials [2,4,5], the frequency and severity of reactogenicity symptoms were higher after the second dose of vaccine than the first one except for vomiting and diarrhoea, which were generally similar regardless of dose. For all age groups, fatigue, headache and new/worsened muscle pain were most common.

Some recent studies have highlighted that a single dose of Pfizer-BioNTech vaccine elicited rapid immune response in vaccined individuals with pre-existing immunity, and with post-vaccination antibody titers similar to or higher than those seen in naive participants who received two doses of vaccine [8]. The authors of study also suggested that the vaccine systemic reactogenicity after the first dose was more pronounced in people with pre-existing immunity and appeared to be similar to the side effects reported for the second dose in phase III vaccine trials [2]. These data, combined with current knowledge of the immunological response to SARS-Cov-2 and the phenomena of reinfection, have led to a recent modification of the vaccination strategy in France. According to the French Health Authority, people with a medical history of COVID-19 should receive only one (mRNA or adenovirus-vectored) vaccine dose except for immunocompromised patients (2 doses of vaccine) [9].

Some limitations should be highlighted. All data collected were self-reported. History of positive SARS-CoV2 serology was also self-reported. It cannot be ruled out that subjects with an asymptomatic and undocumented form of COVID-19 were erroneously included in the "naive patients" group. Furthermore, the serology alone is not a sufficient marker of protection. It only attest contact with SARS-CoV-2. Neutralizing antibodies titration may provide evidence of a protective humoral response. However, this test was not performed in our study. In addition, the small sample size of participants with a history of COVID-19 should lead to caution in interpreting the results.

To conclude, we found that vaccine recipients experienced more frequent reactogenicity after a first dose of the Pfizer-BioNTech COVID-19 vaccine compared to naive individuals. Further studies are needed to confirm these results.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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