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Short Communication

Prevalence and Safety of COVID-19 Vaccination in Community-Dwelling People with Dementia: Findings from a Tertiary Memory Clinic in Italy

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Abstract. This study aimed to explore the prevalence and safety of SARS-CoV-2 vaccination in individuals with dementia. Patients with mild cognitive impairment or dementia were recruited at a tertiary memory clinic, from March 15 to September 15, 2021. Information on COVID-19 vaccination and adverse events experienced after vaccine administration were collected from caregivers. Two-hundred-seventy subjects were finally recruited. Among them, 253 (93.7%) had received the vaccine and only 69 (27.3%) experienced adverse events. Cognitive and behavioral changes following immunization were only rarely reported. COVID-19 vaccination is safe and well-tolerated in patients with cognitive impairment who should be prioritized in the vaccination campaign.

Keywords: Cognitive impairment, COVID-19, dementia, SARS-CoV-2, vaccination, vaccines

INTRODUCTION

The coronavirus disease 19 (COVID-19) pandemic is having a dramatic effect on people with dementia. Indeed, high hospitalization and fatality rates have been observed in cognitively impaired people, and several studies reported dementia among the main risk factors for severe COVID-19 [1, 2]. The higher lethality of the SARS-CoV-2 infection in people with dementia may be explained by the fact that cognitively impaired individuals are generally older, more frail and less likely to be admitted to intensive care units, further reducing their chance of survival [3]. The presentation of COVID-19 with atypical and misleading clinical manifestations (e.g., delirium,

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worsening of behavioral disturbances) may also have contributed to an unfavorable disease course in these patients [4].

It is widely demonstrated that vaccines are among the most effective tools for reducing the spread and mortality of COVID-19 [5]. Accordingly, since the beginning of the vaccination campaign, some stakeholders supported the prioritization of individuals with dementia for vaccination against SARS-CoV-2 [6]. Nevertheless, it has been previously shown that individuals with cognitive impairment have a lower likelihood to receive vaccinations (e.g., the flu and pneumococcal vaccine) compared to their cognitively unimpaired counterparts [7, 8]. Few reports exist of a worsening, albeit transitory, of cognitive or behavioral symptoms in cognitively impaired people after vaccine administration [9]. However, the adverse effects related to vaccination may be underestimated due to communication barriers. Another factor that limits the possibility of ascertaining the safety and tolerability of vaccines in people with dementia is that they are often underrepresented in registration randomized clinical trials (RCTs) [10]. For instance, in the RCTs that led to the approval of the currently commercialized vaccines against SARS-Co-V-2, the number of enrolled participants with dementia was either not reported or extremely low (Table 1). It is therefore imperative to collect "real world" data for exploring the efficacy and safety profiles of COVID-19 vaccines in people with dementia to foster their evidence-based use and contrast vaccine hesitancy [11].

Based on these premises, the present study aimed to 1) evaluate the prevalence of COVID-19 vaccination among people with mild cognitive impairment (MCI) or dementia attending a university memory clinic; 2) estimate the incidence of adverse events in this population; and 3) identify the most common adverse events related to vaccination, with particular focus on cognitive and behavioral effects.

METHODS

Study design and population

A single-center, cross-sectional study was conducted at the Center for Cognitive Disorders and Dementia of the Department of Human Neuroscience, Sapienza University of Rome. We consecutively enrolled individuals with MCI or dementia attending the service from March 15, 2021, to September 15, 2021, according to the following inclusion criteria: 1) diagnosis of MCI or dementia, according to the criteria of the National Institute on Aging and the Alzheimer's Association [12, 13], and 2) presence of a formal or informal caregiver capable of providing reliable information on the patient.

Reporting of COVID-19 vaccination and related side effects

A questionnaire was designed to collect information on previous SARS-CoV-2 infection and vaccination. The questionnaire included 15 questions about previous SARS-CoV-2 infection, COVID-19 vaccination status, type of vaccine received, and short-term adverse events experienced after the administration of the first and second dose of the vaccine. Special attention was paid to possible change in patients' cognitive and behavioral status (e.g., worsening in cognition, occurrence of new behavioral disturbances, or worsening of pre-existent neuropsychiatric symptoms) after receiving vaccination. The questionnaire was administered to caregivers after giving their informed consent to participate in the study.

In the timeframe covered by the present analysis, the vaccines commercialized in Italy were BNT162b2/Comirnaty, mRNA-1273/Spikevax, AZD1222/Vaxzevria, and JNJ-78436735/Johnson & Johnson. The proportion of people who had completed the COVID-19 vaccination in the country ranged between 3.6% (March 15, 2021) and 65.8% (September 15, 2021) [14].

Other variables of interest

Clinical information about the sociodemographic (age, sex, education), cognitive (dementia subtype diagnosis, established according to international criteria, and Mini-Mental State Examination [MMSE] [15] score) and functional (Activities of Daily Living [ADL] [16] and Instrumental ADL [IADL] [17] scores) characteristics of the enrolled patients were also retrieved from their clinical charts.

Statistical analysis

First, we estimated the prevalence of COVID-19 vaccination and the incidence of adverse events following vaccine administration in the recruited population. The most common side effects were described and categorized into the following three

Table 1
Enrollment of participants with dementia in phase III clinical trials testing COVID-19 vaccines

Vaccine Manufacturer(s)	N of participants	Mean/median age (age range)	Dementia as an exclusion criterion	N participants with dementia (%)
BNT162b2 [21] BioNTech, Pfizer	37,706	52.0 (16–91)	No	18 (<0.1%)
mRNA-1273 [22] Moderna	30,351	51.4 (18–95)	No	Not reported
JNJ-78436735 (Ad26.COV2.S) [28] Johnson & Johnson	43,783	52 (18–100)	Yes*	Not reported
AZD1222 (ChAdOx1 nCoV-19) [29] Oxford, AstraZeneca	32,379	51 (18–100)	No	15 (<0.1%)
BBV152 [30] Bharat Biotech	25,753	41.0 (18–97)	No	Not reported
CoronaVac [31] Sinovac	10,214	45 (18–59)	No	Not reported
BBIBP-CorV [32] Sinopharm	38,206	36.1	No	Not reported
Gam-COVID-Vac [33] Gamaleya Research Institute	21,977	45.3	No	Not reported
NVX-CoV2373 [34] Novavax	14,039	56 (18–84)	Yes	None

*only at the Stage 1a and 2a of the enrollment.

subgroups: "general", "cognitive", and "behavioral" effects.

Then, the study population was divided into two groups "Adverse Events" and "No Adverse Events" according to the reporting of any clinical disturbance following the vaccination. The characteristics of the two study groups were compared by adopting the chi-square test for categorical variables and the Mann-Whitney test for continuous variables (as they were not normally distributed). The Kolmogorov-Smirnov test was used to verify the normal distribution of continuous variables. The level of statistical significance was set at 0.05. The variables found to be statistically significant at descriptive analyses were included in a binary multivariate logistic regression model, adjusted for age, sex, and education, adopting the occurrence of adverse events as the dichotomous dependent variable of interest.

Finally, we considered individuals who were administered two vaccine shots and compared the occurrence of general adverse events after the first and second dose adopting the chi-square test. Furthermore, a binary multivariate logistic regression was performed to examine the relationship between the onset of general side effects after the first dose and after the second dose (dichotomous dependent variable of interest), adjusting for sociodemographic variables (age, sex, education), dementia diagnosis, MMSE, ADL, and IADL. The same analyses were performed for behavioral and cognitive adverse events.

The statistical analysis was performed using the Statistical Package for Social Science (SPSS) version 27.

Ethics statement

This study was performed in line with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Policlinico Umberto I University Hospital.

RESULTS

A total of 270 individuals (61.8% women) with MCI (17.3%) or dementia (82.7%) were recruited in the study. Enrolled patients had a mean age of 77.7 (standard deviation [SD] 7.3) years and a mean education level of 10.0 (SD 6.8) years. The most prevalent dementia subtypes were Alzheimer's disease (59.0%), mixed dementia (8.4%), and Lewy body dementia (7.7%). Overall, recruited patients exhibited a moderate cognitive and functional impairment, with mean MMSE, ADL, and IADL scores of 18.8 (SD 6.6), 4.4 (SD 1.9), and 3.6 (SD 2.7), respectively.

At the time of the examination, 17 (6.3%) of the enrolled individuals had presented the SARS-CoV-2 infection.

Two-hundred-fifty-three patients (93.7%) had received the COVID-19 vaccine; among them, 217 (80.4% of the total sample) had completed the two-dose vaccination, while 36 (13.3%) had only received one vaccine shot. The received vaccines were BNT162b2/Comirnaty (73.5%), mRNA-1273/Spikevax (16.6%), and AZD1222/Vaxzevria (9.9%). Among the 17 individuals who did not receive the vaccination, six had previous COVID-19 infection; no information is available on the reason for the non-vaccination of the other 11 subjects.

A large proportion of the vaccinated population (71.9%) did not experience any adverse events. The most common side effects were arm pain (6.71% and 4.6% of patients after first and second dose, respectively), fever (1.58% and 5.52%), and fatigue (1.18% and 3.68%). The most observed adverse behavioral change after vaccination was irritability, experienced

by three (1.18%) patients after the first and five (2.3%) patients after the second dose. Moreover, after the second vaccine shot, two patients experienced depression and hallucinations, while only one experienced agitation. Cognitive adverse effects were ever rarer, with only 0.8% and 1.8% of the study population experiencing a worsening of cognitive impairment after the first and second dose. It was not possible to establish a causal relationship between such behavioral and cognitive modifications and the vaccine administration; however, it is noteworthy that all the reported events were transient, fully resolved within a few days, and did not require hospitalization or pharmacological interventions. The general, cognitive, and behavioral adverse events experienced by the study population after the administration of the first and second dose of the vaccine are detailed in Fig. 1.

The characteristics of patients who did and who did not experience adverse events were substantially similar; indeed, no differences were found regarding sex, age, education, dementia diagnosis, and functional status between the two subgroups (Table 2). The only statistically significant difference was in the severity of cognitive impairment as measured by the MMSE, with patients presenting vaccine side effects exhibiting higher MMSE scores (20.3, SD 6.6 versus 18.3, SD 6.5; $p = 0.04$). However, in the logistic regression model adjusted for sociodemographic variables, the association between MMSE score and adverse events was no longer statistically significant (OR 1.05, 95%CI 0.99 – 1.10, $p = 0.09$) (data available upon request).

We also observed that the proportion of individuals experiencing general adverse events following the second vaccine dose was higher among those who experienced such effects after the first dose relative to those who did not report any effect (63.2% versus 13.7%, $p < 0.001$). Accordingly, in the multivariate logistic regression, the occurrence of general side effects after first dose administration was associated with an increased risk of experiencing general adverse events after the second dose (OR 14.41, 95%CI 3.14 – 66.25, $p < 0.001$). No association was instead found with cognitive and behavioral side effects after first and second dose administration (data available upon request).

DISCUSSION

To the best of our knowledge, the present study represents the first attempt to evaluate the prevalence of COVID-19 vaccination and to describe the short-term adverse events following vaccine administration among individuals with cognitive impairment attending a memory clinic.

Encouragingly, most patients attending our memory clinic were vaccinated at the time of the survey and did not present any vaccine-related adverse events. Specifically, behavioral changes and cognitive worsening only rarely followed vaccination.

At the time of the study conclusion, the vaccine coverage (i.e., the proportion of people who had received two vaccine doses) in the Italian population aged > 12 years was 76.9% [18]. In patients aged 60–69, 70–79, and 80+, the percentage of individuals who had received two vaccine shots was 85.3%, 89.5%, and 92.5%, respectively [18]. The share of patients enrolled in our study in the above-mentioned age groups who had completed the vaccination was 50.0%, 75.7% and 93.1%, thus lower than that observed in the general population. This could reflect the fact that, in Italy, dementia was not included among the conditions prioritized for vaccination [19]. Consequently, most patients received the vaccination at the same time, or even later, than their same-aged cognitively intact counterparts. This finding is also in line with the previous evidence of lower flu and pneumococcal vaccination rates in people with dementia [7, 8].

The incidence of adverse events following vaccination was substantially low. As in the cognitively intact population, the most frequently reported negative effects were mild local and systemic disturbances (e.g., pain at the injection site, fever, fatigue) and their occurrence was more frequent after the second dose. The overall incidence of adverse reactions was higher than that registered by the Italian National Pharmacovigilance Network. As of September 26, 2021, an adverse event reporting rate of 475 reports per 100,000 administered doses was documented in the 60 + population living in the country [20], while the estimate rate of adverse events in our study would theoretically be of 17,872 events per 100,000 administered doses. On the contrary, the frequency of adverse events documented in our population was extremely lower than that reported in phase III RCTs testing COVID-19 vaccines. For instance, local pain, headache, and fatigue occurred after the second vaccine dose in 66%, 39%, and 51% of older participants (i.e., 55+) recruited in the BNT162b2/Comirnaty trial [21] and 83.2%, 46.2%, and 58.3% of older subjects (i.e., 65+) participating to the mRNA-1273/Spikevax trial [22]. These side effects were reported only for

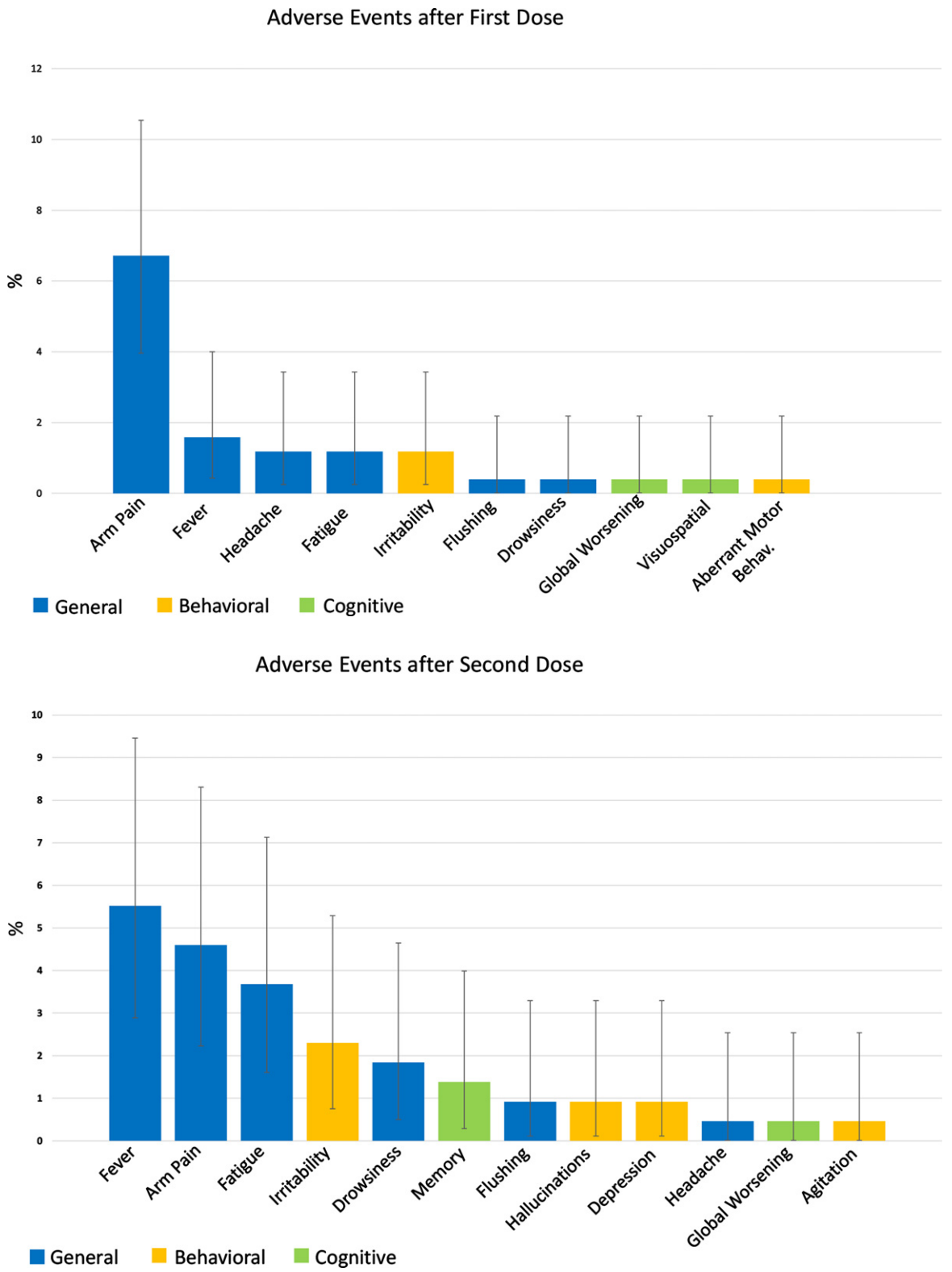

Fig. 1. Adverse events after COVID-19 vaccination in the study population. The two bar plots represent the adverse events experienced by patients after the first (253 patients) and second (217 patients) vaccine dose. Data are shown as %.

Table 2
Characteristics of the enrolled patients who received the COVID-19 vaccination according to occurrence of adverse events immunization. Data are shown as mean ± standard deviation or n (%)

	Overall ($n = 253$)	No adverse events ($n = 182$)	Adverse events ($n = 69$)	p
Sex (%F)	156 (61.7%)	116 (63.7%)	40 (58.0%)	0.46*
Age (y)	77.8 ± 7.3	78.1 ± 7.3	77.2 ± 7.3	0.46§
Education (y)	10.0 ± 6.9	10.1 ± 7.6	9.9 ± 4.5	0.74§
Diagnosis (%)#				0.43*
MCI	38 (16.4%)	24 (14.1%)	14 (22.6%)	
Dementia	196 (83.6%)	147 (85.9%)	49 (77.4%)	
AD	142 (60.3%)	107 (62.4%)	35 (54.8%)	
Vascular	8 (3.4%)	7 (4.1%)	1 (1.6%)	
MixDem	20 (8.6%)	12 (7.1%)	8 (12.9%)	
FTD	5 (2.2%)	4 (2.4%)	1 (1.6%)	
PDD	2 (0.9%)	1 (0.6%)	1 (1.6%)	
LBD	18 (7.8%)	15 (8.8%)	3 (4.8%)	
CBD	1 (0.4%)	1 (0.6%)	0 (0%)	
MMSE	18.8 ± 6.6	18.3 ± 6.5	20.3 ± 6.6	0.04§
ADL	4.5 ± 1.9	4.4 ± 1.9	4.6 ± 1.9	0.33§
IADL	3.7 ± 2.7	3.7 ± 2.7	3.8 ± 2.7	0.72§

*Chi-square test; § Mann-Whitney test. #Missing data: $n = 19$. No information about adverse events was available for two vaccinated patients. AD, Alzheimer's disease; ADL, Activities of Daily Living; CBD, cortico-basal degeneration; FTD, frontotemporal dementia; IADL, Instrumental Activities of Daily Living; LBD, Lewy body dementia; MCI, Mild Cognitive impairment; MixDem, mixed dementia; MMSE, Mini-Mental State Examination; PDD, Parkinson's disease dementia.

4.6%, 0.5%, and 3.7% of patients in our analysis. Along the same lines, the observed incidence of fever after the second dose (i.e., 5.5%) was approximately half of that documented in these RCTs (10–11%) [21, 22]. These findings are strongly suggestive for under-detection and underreporting of adverse events in people with dementia. Indeed, it is well established that pain and other subjective complaints (e.g., fatigue), potentially constituting side effects of many medications, are less frequently reported (and, thus, often poorly managed) by patients with impaired cognition [23, 24]. However, the accurate and timely detection of pain resulting from the COVID-19 vaccine in these individuals is important as it may be easily resolved with the administration of paracetamol or other painkillers. Conversely, its persistence can exacerbate and/or trigger behavioral disturbances and further increase the discomfort of the patient as well as the caregiver's burden. The rate of under-detection of pain and other side effects is likely influenced by the severity of cognitive deficits. In this regard, in our study, subjects reporting the occurrence of any adverse events seem to have a tendency towards a better overall cognitive performance relative to those not exhibiting adverse reactions. Another factor that may have contributed to an underestimation of adverse events in our study is the full reliance on the perspective of caregivers, who may not be completely aware of all the symptoms experienced by the assisted patients. Finally, we have no information about the exact time interval between vaccination and data collection. However, we can hypothesize that, in some cases, the interview took place weeks after the vaccination, when the memory of side effects might have faded.

Some limitations of the present study should be acknowledged and discussed. First, the absence of a control group hampered the possibility of comparing the findings observed in cognitively impaired patients with that potentially documented among healthy controls. Moreover, we only considered short-term side effects of COVID-19 vaccination (thus not focusing on possible long-term reactions) without clearly defining a time limit between the vaccination and the onset of side effects. Finally, the study was conducted in a single Italian university memory clinic and considered a limited number of outpatients. Accordingly, the study results may not apply worldwide to all people living with dementia and to all care settings. For instance, different figures of vaccination prevalence and tolerability could be observed among institutionalized patients. However, despite an isolated report

of higher mortality rates after BNT162b2/Comirnaty vaccine administration in older people living in Norwegian nursing homes [25], other studies showed good efficacy and tolerability of the same vaccine in institutionalized patients [26, 27].

Conclusions

Overall, the present study indicates that COVID-19 vaccination was safe and well-tolerated in patients with cognitive impairment attending an Italian tertiary memory clinic. Given the limitations of our analysis, further studies are needed to confirm our results in other clinical settings and countries.

However, considering the high risk of experiencing adverse outcomes in the event of SARS-CoV-2 infection and the apparently favorable safety/tolerability profile of available vaccines, people with dementia should be prioritized in the vaccination campaign.

DISCLOSURE STATEMENT

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/22-0077r1).

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