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Effectiveness of Post-Exposure Prophylaxis in Preventing Severe SARS-Cov2 Disease (PEP-VAX)

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Abstract

COVID-19 vaccination campaign in Italy primarily focused on preventing epidemic clusters between guests and workers in nursing homes. Despite the administration of the first vaccine dose, two epidemic clusters burst few days after vaccination: the short latency between vaccine inoculation and symptoms manifestation suggests that infection could be already occurred before the first vaccine dose. In this study we enrolled 149 patients from four different nursing homes that were comparable two by two about medical assistance features, age and clinical complexity of guests. Two of these facilities received the first vaccine dose shortly before the onset of the epidemic clusters, which resulted in a significantly reduced morbidity and mortality rate. The aim of the study is to define the principal risk factors associated to severe COVID-19 disease and to evaluate the impact of a potential post-exposure prophylaxis on SARS-CoV-2 infection mortality rate.

Keywords: Covid; Post esposure prophilaxis; Ring vaccination

Introduction

During the first wave of SARS-CoV-2 pandemic, 9,1% of elderly people inside Nursing Homes died [1]. Though non homogeneous among different regions of Italy, this mortality rate is much higher than that of the general elderly Italian population. From an ISS (Istituto Superiore di Sanità) survey, the peculiar vulnerability of Nursing Home patients is due to multiple organizational factors among which: absence of ad-hoc guidelines for infection prevention and treatment, the impossibility to isolate guests with a certain or suspected COVID-19 infection, a poor vaccination coverage against influenza virus, lack of a sufficient number of health care workers, difficulties of transferring infected guests to hospitals or other secondary care facilities, lack of personal protective equipment and drugs, and the impossibility to carry out nasopharyngeal swabs [1].

We carried out this study in Emilia-Romagna, where nursing homes hosting more than 5% of their hosts infected with COVID-19 have been converted to COVID-19 nursing homes. Guest's clinical evaluation and treatment in these COVID-19 nursing home is similar to that of COVID wards in the hospital, with drugs supplies coming from the local hospital pharmacy. Data from the pre-COVID-19 era show a high mortality and morbidity rate in these structures, mainly due to the multiple morbidities and the infective risk factors of their hosts. Due to their peculiar vulnerability, in programming its national vaccination campaign, Italy classified nursing home guests as priority patients to receive the vaccine, because of their fragility and high infective risk.

The first phase of the vaccination campaign in Italy started in December 2020. It included guests and workers inside nursing homes, in order to decrease their morbidity and mortality rate.

During the vaccination campaign in Romagna nursing homes, two epidemic clusters burst few days after the administration of the first vaccine dose. The manifestation of these epidemic clusters has offered the possibility to observe the incidence of COVID-19 infection and the progression of the disease in a population

category to whom the first vaccine dose was already administered. Patients in nursing homes with similar organizational features, who got infected with COVID-19, but to whom no vaccine was yet administered, were classified as controls.

The analysis of clinical results observed in these nursing homes allows to evaluate the effects of different epidemiologic risk factors (associated to the morbidity and mortality of the virus) on elderly patients who were wither non vaccinated, or who received only one vaccine dose. The findings show that Pfizer/Moderna mRNA (messenger ribonucleic acid) vaccines efficacy (VE) was insignificant until two weeks after vaccination, increasing over the next week to 43% at 14-20 days [2]. Moreover it has been observed that SARS-CoV2 vaccines based of vector Ad5 were able to induce a T-cell and humoral response after 14 days of inoculation [3]. However, RNA vaccine BNT162b1 showed a low siero-conversion before 21 days from the inoculation of the first vaccine dose [4]. There is paucity of literature describing from a clinical point of view the progression of SARS-CoV-2 disease in patients with a positive nasopharyngeal swab immediately after the administration of the first vaccine dose, which is one of the aims of our study.

Methods

We conducted a retrospective, observational, epidemiologic study. We recruited 149 patients, hosted in four nursing homes of Emilia-Romagna. We observed patients from January 2021 to March 2021. Two patients were excluded from the study since they had already contracted COVID-19 infection.

The aim of the study is to evaluate COVID-19 infection mortality rate in nursing homes monitored during their epidemic COVID disease cluster, and to point out the principal risk factors associated to severe COVID-19 disease or to the death of the patients.

The end-points of our study are:

- Number of positive (pathological) nasopharyngeal swabs in the included nursing homes in the study period
- Number of symptomatic patients in the included nursing homes in the study period
- Mean duration of symptoms of COVID-19 disease
- Number or deceased guests in the included nursing homes in the study period

Patients were classified as affected by COVID-19 infection in case of a pathological nasopharyngeal swab analyzed with rt-PCR technique or in case they showed symptoms compatible with the disease in the presence of epidemiologic risk factors for SARS-CoV2 infection. The four nursing homes included in the study were similar two by two for what concerns medical assistance features and number, age and clinical complexity of guests. These nursing homes can be classified in two categories as regards assistance needs: those with a low intensity assistance needs, and those with a medium intensity assistance needs. Both of facilities with a low intensity assistance needs were private and licensed nursing homes that offered a limited but similar number of beds (20 vs. 22). Both of structures with a medium intensity assistance needs were licensed nursing homes that were comparable for number of residents (50 vs. 49), even though they differed in occupancy rates (91% vs. 67%).

Hospitalization was decided according to Clinical Frailty Scale (CSF) criteria and to the availability of a sufficient number of healthcare workers and of medical devices, oxygen therapy and drugs. A standardized management protocol was elaborated by the local health authorities to be put in practice in the COVID-nursing homes. These operating instructions have rendered the clinical management of affected patients homogeneous throughout the regional territory. The protocol included periodic nasopharyngeal swabs and daily health status monitoring to both guests and healthcare workers, in order to find out new COVID-19 cases as soon as possible. This was made possible by a strict coordination between nursing homes doctors and specialized equips composed by doctors trained in managing covid patients inside COVID-nursing homes (Territory Assistance Nuclei – NAT), infectious disease doctors, pneumologists, geriatricians, pharmacists, epidemiologists and nurses.

Two of the structures (one with a low and the other with a medium intensity assistance need) received the first vaccine dose just before the onset of symptoms. The kind of vaccine administered, BNT162b2 Pfizer BioNTech, was chosen according to the local availability of vaccine doses in that given period of the year. The vaccine was administered to all nursing home guests who had previously signed the informed consent.

Vaccine inoculation occurred on the same day for all the guests of a given nursing home. Nasopharyngeal swabs were performed to all guests two days before vaccine inoculation, and all turned out to be negative (non pathological). The day of symptoms onset was calculated from the day of onset of any symptoms attributable to COVID-19 infection: fever, desaturation, cough, or crackles at lungs auscultation. The severity of the disease has been calculated utilizing the NIH COVID-19 Disease Severity Score*. The day of clinical recovery corresponds to the day in which we have observed complete regression of all the symptoms attributable to the disease. Patient treatment was carried out following the local healthcare units guidelines on the primary care treatment of patients infected with COVID-19. With this study we want to evaluate if the risk of death or of severe disease is related to risk factors independent from COVID-19 infection, or if it is influenced by the administration of the vaccine.

Statistical analysis

A descriptive statistical analysis has been carried out analyzing the variables registered on the entire set of patients and then separately according to the type of nursing home. All the differences between vaccinated and non-vaccinated nursing homes have been studied, in terms of both basal features and outcomes. Student T test for independent groups, and Chi Squared Test were used. For binary outcomes (infection, hospitalization, death), if significant, vaccination effect was evaluated using a multivariate analysis with a Logistic Regression Model to find out any confounding variables resulted significant in the previous univariate analysis. Significance threshold has been put at 0.05 for all the tests used. The statistical analysis has been carried out with the software STATA 14.2.

Results

The nursing homes in which COVID-19 infection clusters burst, were paired, according to the kind of assistance provided. Two of them were low intensity assistance (34%), and two were medium intensity assistance (66%). The mean age of the patients was 85.6 years (SD 8.8). Females represented 68.7% of the patients. The two sets of nursing homes shared a similar mean age and sex distributions. All the included patients were elderly people affected by numerous chronic diseases. Specifically, the health conditions of the patients prior to the infection were superimposable among the studied nursing homes, and were characterized by physical or cognitive deficits, lack of independence in the activities of daily living, bed confinement and altered consciousness. However, all of them were stable from a clinical point of view, without the need of hospitalization.

Before the appearance of the COVID outbreak the first dose of vaccine was administered to 73 patients (49.7% of the studied population), of whom 26 (52%) belonged to a low intensity assistance nursing home and 47 (48.5%) to a medium intensity assistance one. Symptoms of infection manifested from the 2nd to the 21first day after the inoculation, with a median of 12 days (IIQ 7-15 days). The outbreak in the medium intensity nursing home manifested previously (from the second day after the vaccination, with a median of 8) with respect to the one in the low intensity assistance nursing home (from the tenth day after vaccination, with a median of 15–Mann-Whitney Test, p=0.0002). The molecular nasopharyngeal swab resulted positive in 93.9% of the patients, but among the two kinds of structures the low intensity ones had fewer infected patients than the medium intensity ones (88% versus 96.9%, p=0.03). Patients with symptoms compatible with COVID-19 infection were 104 (70.8%). Two of them were never positive to the seriated nasopharyngeal swabs. The most common symptoms were fever (54.4%) and pneumonia (49.7%). Symptoms lasted from 1 to 34 days, with a mean of 9.5 days (SD 7.4).

Low intensity nursing homes patients were significantly less symptomatic (54%) with respect to the medium intensity ones (79.4%) (p=0.001). As far as disease severity is concerned, mild disease manifested in 18 cases (12.2%), moderate disease in 23 cases (15.7%), severe disease in 28 cases (19.1%), and critical disease in 35 cases (23.8%). Medium intensity assistance nursing homes experienced more cases of critical disease (30.9%) than the low intensity ones (10%) (p=0.006). 58 patients (39.5%) needed hospitalization, and 38 patients (25.9%) died. The two kind of nursing homes differed also in terms of mortality percentage: 12% in the low intensity assistance, 33% in the medium intensity assistance (p=0.006) (Table 1).

Variable	Low intensity (n=50)	Medium intensity (n=97)	Total (n=147)	
	media (ds)			p (t-test)
age (years)	84.7 (10.4)	86.1 (8.0)	85.6 (8.8)	0.371
Symptoms latency post vaccination (days)	15.4 (2.9)	10.2 (4.3)	11.7 (4.6)	0.0001
Disease duration (days)	9.6 (7.1)	9.4 (7.6)	9.5 (7.4)	0.932
	n (%)			p (test chi2)
Male sex	15 (30.0)	31 (32.0)	46 (31.3)	0.808
Vaccination	26 (52.0)	47 (48.5)	73 (49.7)	0.684
Positive nasopharyngeal swab	44 (88.0)	94 (96.9)	138 (93.9)	0.033
Symptoms onset	27 (54.0)	77 (79.4)	104 (70.8)	0.001
Hospitalization	17 (34.0)	41 (42.3)	58 (39.5)	0.331
Death	6 (12)	32 (33.0)	38 (25.9)	0.006

Severity score	1 (mild)	4 (8)	14 (14.4)	18 (12.2)	0.006
	2 (moderate)	8 (16)	15 (15.5)	23 (15.7)	
	3 (severe)	10 (20)	18 (18.6)	28 (19.1)	
	4 (critical)	5 (10)	30 (30.9)	35 (23.8)	

Table 1: Descriptive and comparative analysis of the two kind of structures.

Nursing homes who received the vaccine had less cases of COVID-19 infection demonstrated by a positive nasopharyngeal swab (90.4% versus 97.3%), but this data is not statistically significant (p=0.08). Among vaccinated and non-vaccinated guests, symptoms manifested in a similar percentage of people and had a similar duration, too. However, if the severity of the disease is taken into account (mild, moderate, severe or critical) vaccinated hosts experienced less frequently the critical form of the infection (9.6%) with respect to non-vaccinated ones (37.8%) (p=0.001). Moreover, among vaccinated people, Sp02 minimal values are higher (91.7 vs 89.6, p=0.036), CRP values are lower (52.7 vs 118.7, p=0.024), and lactate values are lower (241.7 vs 318.7, p=0.018).

There were significantly less deaths among vaccinated people with respect to the non-vaccinated ones (11% vs 40.5; p<0.0001) (Table 2). Analyzing the mortality rate, the vaccinated low intensity assistance nursing home experienced the lowest mortality rate (3.9%), while the non-vaccinated medium intensity assistance nursing home was the one in which the mortality rate was higher (49%) (Figure 1).

		vaccinated (n=73)	**non vaccinated (n=74)**	**total (n=147)**	
Variabiles		media (ds)			p (t-test)
age (years)		85.4 (9.8)	85.8 (7.9)	85.6 (8.8)	0.814
Disease duration (days)		8.9 (6.9)	10 (8)	9.5 (7.4)	0.474
SpO2 lowest value		91.7 (5.4)	89.6 (6.0)	90.7 (5.8)	0.036
CRP		52.7 (57.0)	118.7 (136.2)	90.6 (113.8)	0.024
LDH		241.7 (61.7)	318.7 (147.0)	284.9 (122.8)	0.018
lymphocytes		1077.3 (747.7)	1024.7 (483.8)	1046.8 (603.4)	0.737
		n (%)			p (test chi2)
Male sex		27 (37.0)	19 (25.7)	46 (31.3)	0.139
Positive nasopharyngeal swab		66 (90.4)	72 (97.3)	138 (93.9)	0.082
Symptoms onset		52 (71.2)	52 (70.3)	104 (70.8)	0.898
hospitalization		24 (32.9)	34 (46.0)	58 (39.5)	0.105
death		8 (11.0)	30 (40.5)	38 (25.9)	<0.001
Disease severity score	1 (mild)	11 (15.1)	7 (9.5)	18 (12.2)	0.001
	2 (moderate)	15 (20.6)	8 (10.8)	23 (15.7)	
	3 (severe)	19 (26.0)	9 (12.2)	28 (19.1)	
	4 (critical)	7 (9.6)	28 (37.8)	35 (23.8)	

Table 2: Descriptive and comparative analysis of vaccinated and non-vaccinated group.

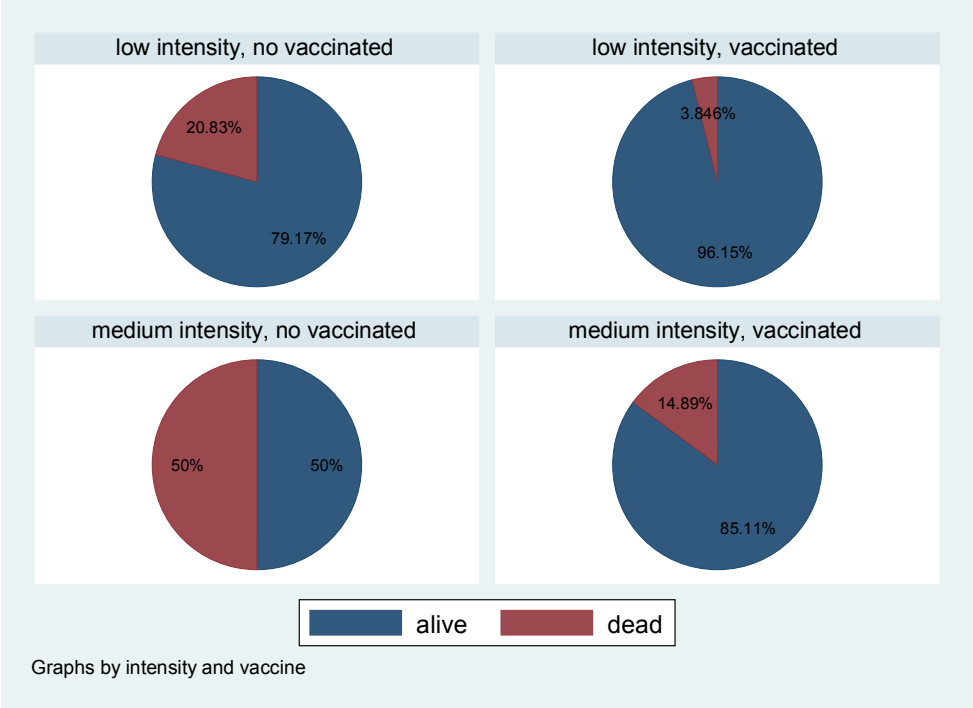

Figure 1: Comparative analysis of deaths in the four studied nursing homes.

The time span between the vaccination and symptoms onset did not result to have a statistically significant relationship with mortality (Table 3).

	alive (n=109)	**dead (n=38)**		
Variabiles	media (ds)		p (t-test)	**OR (IC 95%)**
age (years)	84.9 (8.9)	87.8 (8.5)	0.082	1.04 (0.99-1.09)
Symptoms latency post vaccination (days)	12.0 (4.7)	10.1 (4.2)	0.306	0.91 (0.77-1.09)
	n (%)		p (test chi2)	
Male sex	31 (28.4)	15 (39.5)	0.207	1.64 (0.76-3.55)
Medium intensity assistance nursing home	65 (59.6)	32 (84.2)	0.006	3.61 (1.39-9.36)
vaccination	65 (59.6)	8 (21.1)	<0.001	0.18 (0.08-0.43)

Table 3: Univariate analysis of risk factors influencing death rates.

In the multivariate logistic regression model for the study of risk factors linked to death rate, the ones which were statistically significant were age (OR= 1.1. 95% CI 1-1.2), medium intensity assistance nursing home (OR=4.2. 95% CI 1.5 – 11.9), male sex (OR=4.1. 95% CI 1.4 – 12.1) and administration of the first dose of anti-COVID vaccine (OR=0.1. 95% CI 0.04 – 0.3) (Table 4).

	OR	95%confidenceinterval	p
vaccination	0.11	0.04-0.30	<0.001
age (years)	1.1	1.03-1.18	0.006
Male sex	4.14	1.42- 12.10	0.009
Medium intensity structures	4.18	1.47-11.90	0.007

Table 4: Multivariate analysis on risk factors influencing death rates.

Discussion

This study took origin from the observation that in nursing homes where BNT162b2 Pfizer BioNTech vaccine was administered involuntarily in the immediate post-exposition phase, patients infected with COVID-19 had a less ominous clinical outcome. The disease course was less severe in terms of both symptoms duration, intensity and mortality rate.This study highlights how the degree of assistance of hosts of nursing homes and the COVID-19 vaccination are two pillars in determining patients prognosis in case of SARS-CoV2 infection. As far as assistance level is concerned, it is logic that the higher the degree of assistance need, the higher are the comorbidities of hosts residing in these kind of structures. Though being homogeneous in terms of age, medium intensity nursing homes' guests are in a greater assistance needs, therefore more fragile and more comorbid with respect to low intensity nursing homes' guests. However, it was not possible to utilize more specific data to determine the degree of comorbidities of the patients of the two kinds of nursing homes. This represents a study limitation.

The comparison between clinical end-points between vaccinated and non-vaccinated guests allows to verify the efficacy of vaccination in the immediate post exposure time span. The primary end-point evaluates if the risk of disease and death is linked to factors which are independent from the infection, or if it is correlated to vaccination or timing of vaccination after viral exposure. The hypothetical date in which patients contracted the disease was calculated taking into account the average disease latency. The intent was to observe if an early post-exposure vaccination were able to confer a higher disease protection. The secondary end-point was to evaluate if a single Pfizer dose were sufficient for Covid-19 protection. Serological parameters that quantify disease severity and progression were also examined (CRP, LDH, total lymphocytes count) in hospitalized patients, in order to evaluate the vaccination impact on surrogate elements of disease severity. Hospitalization rate was not considered in the analysis because it was linked not only to clinical factors, but also to the level of assistance the nursing homes were able to provide to their guests: patients were hospitalized in case of clinical deterioration or in case the nursing home was not able to provide an adequate number of healthcare workers specialized in assisting COVID patients. We compared disease incidence and clinical outcome among nursing homes guests, evaluating if the risks of infection and mortality are correlated to vaccination and to the timing of it with respect to the date of exposure to the virus, or if these risks are linked to factors which are independent from the vaccination.

The timing of vaccine administration with respect to the hypothetical disease contraction date, was calculated starting from latency of symptoms onset, with the intent to observe if a precocious post-exposure vaccination were able to confer a higher protection. The second and most important data is the one representing protection conferred by the vaccine against severe or critical disease, and death. Although symptoms manifestation and disease duration were similar among vaccinated and non-vaccinated patients, if the severity score of the disease is taken into account (mild, moderate, severe, critical), it is astoundingly significant how critical disease in vaccinated patients is less prevalent. The second vaccination dose was never administered since all the patients contracted the disease after the first dose.

Conclusion

Vaccine administration immediately after, or with a relative latency, after virus exposition, determines a significant reduction in mortality and disease severity, independently from the level of assistance of the nursing home. This study cannot indeed be considered as a reference to clarify the role of the vaccine for infection prevention (which has already been demonstrated by many efficacy studies [1]), because the latency between vaccine inoculation and symptoms manifestation, shorter than the normal disease incubation period, makes us presume that infection had already happened before immunization. It cannot be excluded that the vaccine confers a higher immune system stimulation compared to contracting the disease naturally. However, it is likely that the vaccine acts in a more precocious way with respect to the disease, so that it confers a level of protection which is comparable to that provided by the administration of monoclonal antibodies. It can therefore be reasonable to propose a post-exposure prophylaxis basing on the model of Ring Vaccination, which was already applied for smallpox pandemic in 1970 and more recently for the Ebola epidemic [5]. Ring Vaccination consists in tracing and vaccinating contacts, and contacts of contacts of a confirmed case, in order to anticipate a protective immunity for the clinical expression of the disease. It would be reasonable to consider the administration of a second vaccine dose after six months have passed from the infection, or in case of a new exposure with people infected with COVID-19.

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