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Evaluation of the anti-COVID-19 vaccination campaign in the Metropolitan Area of Milan (Lombardy Region, Northern Italy)

Valutazione della campagna vaccinale anti-COVID-19 nella ATS di Milano

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WHAT IS ALREADY KNOWN

- **Randomized trials and population-based effectiveness studies in the field show that COVID-19 vaccines are extremely effective in reducing hospitalization and mortality in the general population.**
- **Vaccine coverage in the region of Lombardy exceeds 80%; there are still pockets of vaccine hesitancy.**
- **Among vaccinated subjects, elderly people and patients with certain chronic conditions have a greater risk of hospitalization.**

WHAT THIS STUDY ADDS

- **Certain characteristics increase the risk of not getting the COVID-19 vaccine, for instance residing in severely deprived areas, not being born Italian, and not participating in public health programmes for the reduction of individual risk, such as flu vaccines or organized screenings.**
- **This population-based study, conducted on about 3 million people residing in a greater metropolitan area of Italy, confirms the effectiveness of vaccines in reducing hospitalization and mortality in the field, and also confirms how relevant it is to include in vaccination campaigns subjects with comorbidities or particular sociodemographic profiles.**
- **Among subjects vaccinated with two doses, the risk of hospitalization remains higher in the elderly population and among subjects with specific chronic conditions.**
- **It is essential to use integrated information systems to reinforce existing evidence and accumulate new evidence needed to guide public healthcare action.**

ABSTRACT

OBJECTIVES: to present an evaluation of the campaign for vaccination against COVID-19 in the territory covered by the Agency for Health Protection of the Metropolitan Area of Milan from 01.01.2021 to 30.09.2021.

DESIGN: descriptive study of vaccine adherence; predictive study of the factors associated with vaccine adherence, efficacy of vaccination in terms of hospitalization and mortality, and factors that increase the risk of hospital admission following full vaccination.

SETTING AND PARTICIPANTS: population-based study with subjects aged >18 years eligible for vaccination (N. 2,981,997). An information system obtained by integrating various administrative healthcare sources made it possible to analyse socioeconomic characteristics, COVID-19 related hospitalizations, and general mortality in subjects eligible for vaccination.

MAIN OUTCOME MEASURES: full vaccination (2 doses); COVID-19-related hospitalizations, COVID-19-related hospitalizations occurring more than 15 days after the second dose, general mortality.

RESULTS: in the first nine months of the vaccination campaign, 74.7% of the subjects (N. 2,228,915) was fully vaccinated, whereas 15.6% (N. 465,829) did not even receive one dose. Women have a lower probability of getting vaccinated than men; the 50-59 years and 70+ years age groups emerge as the most problematic to reach, while the younger one (<40) is the most adherent. A social gradient emerged, with residents of more disadvantaged areas progressively less incline to get vaccinated than those living in more affluent areas. Adherence is greater in Italian citizenship and is likely to increase with an increase in the number of chronic conditions. Hospitalizations amounted to 1.22% (N. 5,672) in the unvaccinated population compared to 0.05% (N. 1,013) in the vaccinated population; general mortality was 4.51% (N. 15,198) in the unvaccinated population against 0.32% (N. 8.733) in the vaccinated population. Sociodemographic factors and the presence of previous health conditions are important predictors of hospitalization outcomes even within the fully vaccinated population. Specifically, the highest hazard ratios are found in subjects with heart failure (HR 2.15; 95%CI 1.83-2.53), in immunocompromised patients (HR 2.02; 95%CI 1.52-2.69), and in transplant recipients (HR 1.92; 95%CI 1.10-3.33).

CONCLUSIONS: vaccination campaign adherence is affected by the sociodemographic characteristics of the population and is a determining factor in preventing hospitalizations for COVID-19 and death. The persistent higher risk of hospitalization in chronic subjects following the second dose emphasizes the need to direct booster doses to the more vulnerable. Information systems proved to be effective monitoring tools in the absence of specific trials.

Keywords: COVID-19, vaccination, hospitalizations, mortality, sociodemographic factors, informative systems

RIASSUNTO

OBIETTIVI: valutare l'adesione alla campagna vaccinale anti COVID-19 nel territorio dell'Agenzia per la tutela della salute della Città metropolitana di Milano (ATS di Milano) tra il 01.01.2021 e il 30.09.2021.

DISEGNO: studio descrittivo dell'adesione alla vaccinazione; studio predittivo dei fattori associati all'adesione e all'efficacia sul campo della vaccinazione in termini di ricovero e di

mortalità e dei fattori che incrementano il rischio di ricovero tra i vaccinati.
SETTING E PARTECIPANTI: studio di popolazione basato sui residenti di età >18 anni eleggibili per la vaccinazione (n. 2.981.997). L'integrazione di diverse fonti amministrative di ambito sanitario ha permesso di risalire alle caratteristiche sociodemografiche e agli esiti di ricovero per COVID-19 e mortalità generale dei soggetti eleggibili per la vaccinazione.
PRINCIPALI MISURE DI OUTCOME: vaccinazione completa (doppia dose), ricovero per COVID-19, ricovero per COVID-19 oltre 15 giorni successivi alla seconda dose, mortalità generale.
RISULTATI: nei primi nove mesi di campagna vaccinale, si è sottoposto al ciclo completo di vaccinazione il 74,7% della popolazione eleggibile (n. 2.228.915), con il 15,6% (n. 465.829) non sottoposto nemmeno alla prima dose. Le donne hanno una probabilità più bassa di vaccinarsi rispetto agli uomini; le classi di età 50-59 e 70+ emergono come le più problematiche da raggiungere, mentre quella più giovane (<40) risulta la più aderente. Si denota la presenza di un gradiente sociale, con i soggetti residenti in aree più svantaggiate progressivamente meno aderenti rispetto a coloro che vivono in aree più agiate. L'accesso è maggiore nelle persone di cittadinanza italiana e aumenta progressivamente in corrispondenza del numero di cronicità presenti. Gli eventi di ricovero attribuibili a COVID-19 ammontano all'1,22% (n. 5.672) nella popolazione non vaccinata rispetto allo 0,05% (n. 1.013) della popolazione vaccinata; la mortalità generale riguarda il 4,51% (n. 15.198) dei non vaccinati contro lo 0,32% (n. 8.733) dei vaccinati. I fattori sociodemografici e la presenza di problematiche di salute pregresse sono importanti predittori di esiti di ricovero anche all'interno della popolazione sottoposta a doppia dose vaccinale. Nello specifico, gli hazard ratio più elevati si riscontrano nei soggetti con scompenso cardiaco (HR 2,15; IC95% 1,83-2,53), nei pazienti immunocompromessi (HR 2,02; IC95% 1,52-2,69) e nei trapiantati (HR 1,92; IC95% 1,10-3,33).
CONCLUSIONI: l'adesione alla campagna vaccinale risente delle caratteristiche sociodemografiche della popolazione e risulta un fattore determinante nel prevenire le ospedalizzazioni per COVID-19 e i decessi. Il persistente rischio di ospedalizzazione, più elevato nei soggetti cronici, in seguito alla seconda dose mette in evidenza la necessità di indirizzare le dosi booster verso i soggetti più fragili. I sistemi informativi si rilevano efficaci strumenti di monitoraggio in assenza di trial specifici.

Parole chiave: COVID-19, vaccinazione, ricoveri, mortalità, fattori sociodemografici, sistemi informativi

INTRODUCTION

In January 2021, in the area covered by the Health Protection Agency (ATS) of the Metropolitan City of Milan (Lombardy Region, Northern Italy), the vaccination campaign to prevent the effects of COVID-19 infection was launched. After the initial phases, when recipients were healthcare workers, nursing home residents, people aged 80 and over, the police, school and university staff, and frailer individuals, on 2 April, following ministerial guidelines , vaccination was extended to the 75-79 year old age group, on 15 April to people aged 70-74, on 22 April to people aged 60-69, on 15 May to people aged 50-59, and on 13 June to those under 50. Subjects aged 16-29 had access as of 2 June. On 31 May, the Technical Scientific Committee (CTS) of AIFA approved the extension of the indication of the Comirnaty vaccine (BioNTech/Pfizer) for the 12-15-year-old age group. AIFA resolution 111/2021 – published in the GU Serie Generale no.178 dated 27.07.2021 – extended use of the Spikevax (Moderna) vaccine to subjects aged 12 and above.

As indicated by a memo of the Italian Ministry of Health,[1] beginning on 20 September, transplant recipients and immunocompromised patients who had already completed the vaccine cycle were made eligible for a COVID-19 vaccine booster shot. As of 3 October, people over 80 years of age were also eligible to book an appointment for a COVID-19 vaccine booster shot (3rd dose).[2]

Vaccine coverage monitoring is ensured at a national and international level by the Ministry of Health, which provides data daily.[3]

There are to date several trials promoted by the pharmaceutical companies that produce the vaccines.[4-11] All results indicate an efficacy of over 80% – for subjects who have received two doses, the latter of which at least 14 days before – in reducing hospitalization, intensive care admission, and mortality, especially in the categories most at risk. Consistently with these data of vaccination efficacy and safety, both viral vector vaccines and mRNA vaccines were initially supplied. Following substantial evidence of inferior tolerability of viral vector vaccines,[11-13] in Italy, mRNA vaccines were prevalently administered.

Studies carried out in the area covered by ATS of Milan have confirmed that the characteristics most associated with the events of hospitalization and death following COVID-19 infection are concentrated in subjects over 70 years of age with specific chronic conditions.[14-18]

In Italy, to date (12.10.2021), adherence to at least one dose of vaccine is about 85%,[19] with an even greater coverage in Lombardy.[20] Despite the good vaccine coverage (consistent with other European countries), certain segments of the population remain hesitant toward the vaccine[21,22] even in the presence of chronic conditions.[23]

The Italian National Health Institute (*Istituto superiore di sanità*, ISS) assessed vaccine effectiveness at a national level, confirming the clinical trial estimates on the entire

Italian population.[24] However, the information system needed to produce the data required for an evaluation of the entire vaccine campaign, which has by now come to the end of its first phase, is very complex. It is necessary to ensure access to several databases, with the possibility of integrating them using record linkage and with detailed information for each individual which is not always available at a national level.

With respect to the ATS of Milan, assessment of the COVID-19 epidemic was organized with a series of studies which progressively investigated the characteristics of the population infected,[25] described mortality[26] and the kinetics of the epidemic spread,[27] studied the at-risk groups, and evaluated the mitigation actions taken during the various epidemic stages.[28] But, to date, evaluation of the epidemic trend and its effects in the area covered by the ATS of Milan cannot be carried out without evaluating the vaccine campaign both in terms of adherence and health outcomes, focusing in particular on the more vulnerable population.

Aim of this work is to present an overall assessment of the vaccine campaign conducted in a large metropolitan area (3.5 million residents) from which the epidemic began[27] and which, with more than 300,000 cases currently recorded, is one of the hardest hit areas in Italy.[29]

This study also aims to present an evaluation of the following: **1.** the sociodemographics characteristics of the hesitant population compared to the population getting vaccinated; **2.** the effectiveness of the vaccination on a population with specific risk factors and in a real-world context; **3.** the characteristics of the population vaccinated with two doses that was subsequently hospitalized for COVID-19.

MATERIALS AND METHODS

The population included in the study is the population residing in the provinces of Milan and Lodi and served by the ATS of Milan, aged ≥19 years, and alive as of 01.01.2021 (2,981,997). The subjects were followed from inclusion in the study until the end of follow-up on 30.09.2021 and the vaccinations, COVID-related hospital admissions, and deaths for all causes were set within this time frame.

The information coming from the Civil Registry (*Nuova anagrafe regionale*, NAR) of patients was integrated with the information from the permanent georeference system, developed and maintained by the Epidemiology Unit of the ATS of Milan, which makes it possible to integrate the information from the Population and Home Census of 2011 and, in particular, the deprivation index, calculated based on census tract.[30,31] The presence of comorbidities was obtained using the Patient Database (*Banca dati assistito*, BDA) of chronic patients, created following the guidelines and algorithm of the Region of Lombardy.[32,33]

The vital status is updated – with about a week's delay – thanks to integration of municipal registers with the Civil Registry – synchronized daily with the Italian Ministry of Economy and Finance – to which has been added daily synchronization with the funeral home registers activated during the COVID-19 epidemic to accelerate the reporting system of deaths.

The database on active residents/patients at the beginning of the observation period provided by the Civil Registry was further integrated with the vaccination data flow, which records information concerning the two dates of vaccine administration and the type of vaccine administered.

Using the database on outpatient services for organized breast and colorectal cancer screening and the specific database for flu vaccination to subjects over 65, we determined a "prevention propensity", defined as adherence to at least one of the prevention services offered by the ATS of Milan in the period 2017-2019. In detail, we investigated the adherence to flu vaccine administration for subjects over 65 years of age and participation in the breast and colorectal cancer screening for subjects between 50 and 69 years of age. The propensity to take part in prevention campaigns was therefore determined only for subjects aged 50 or older.

Using total integration of all the described sources, with deterministic record linkage using the anonymized individual code present in the data warehouse systems of the ATS of Milan, an information system was created for the evaluation of the vaccine campaign, producing an assessment as of 30 September 2021 (Table S1).

Specifically, four different studies were conducted on the population base of almost 3 million residents (aged 19 or older).

STUDY 1: DESCRIPTION OF VACCINE ADHERENCE

Based on the information obtained using deterministic record linkage of the available databases, the specific adherence to the vaccine programme was described with respect to sociodemographic variables, stratifying the study population into three types of vaccine adherence: **1.** recipients of two doses; **2.** recipients of a single dose; **3.** subjects who were not vaccinated.

STUDY 2: ANALYSIS OF PREDICTIVE FACTORS OF VACCINATION

The sociodemographics, propensity to get vaccinated, and previous COVID-19 diagnosis of fully vaccinated subjects were compared with those of subjects who did not receive vaccination, using unconditional logistic models and estimating the Odds Ratios (ORs) and corresponding 95% confidence intervals (95% CI). Subjects who received a single vaccine dose were not used in this

study design and the following, as they represent a population with extremely heterogeneous adherence issues, ranging from a previous infection – which was not considered an impediment against (or at least a reason for delaying) the second dose from the onset of the vaccination campaign and, in any case, depends on subjects' declarations – to a decision not to get the second dose because of symptoms experienced after the first dose or news referred from the media.

STUDY 3: EFFECTIVENESS OF VACCINATION IN THE FIELD (VACCINATED *VS* UNVACCINATED)

A cohort was formed including unvaccinated subjects and subjects who received two vaccine doses. The time axis for the study is the number of days starting from 1 January 2021 until 30 September 2021. Two different outcomes were considered in the study: **1.** hospital admission for COVID-19; **2.** general mortality.

The analysis investigated the comorbidities more often associated with both hospitalization[17] and mortality[14] for COVID-19 identified in previous studies conducted on the population of the area served by the ATS of Milan. For each of the diseases considered, we estimated the Hazard Ratio (HR) and corresponding 95% confidence intervals (95% CI), using multivariable Cox regression models including the vaccination (date of second dose) as time-dependent variable. The models were adjusted for gender, age, socioeconomic status, nationality (Italian *vs* foreign), previous COVID-19 infection, and presence of comorbidities. Estimates were also made on the study population without comorbidities, along with a total estimate including the same regressors and the number of comorbidities.

For the analysis which had hospitalization as its outcome, the date observation ends is the date of first hospital admission for COVID-19, the date of censoring is 30 September 2021 or death; for vaccinated subjects, only hospital admissions which occurred more than 15 days after the second dose were considered. For the analysis with mortality as outcome, the date of death is the end of observation, and the date of censoring is 30 September 2021.

STUDY 4: PREDICTIVE FACTORS FOR COVID-19 RELATED HOSPITALIZATION IN THE VACCINATED POPULATION

The study included all subjects who received two doses, and outcomes were hospitalizations for COVID-19 which occurred more than 15 days following the second dose. Using multivariable Cox regression, we estimated the Hazard Ratios (HRs) and corresponding 95% confidence intervals in order to identify the predictors of hospitalization for COVID-19 in fully vaccinated subjects. The predictors were then included in the multivariable Cox regression, from which we obtained the HR estimates for individual diseases.

RESULTS

STUDY 1: DESCRIPTION OF VACCINE ADHERENCE

Within the ATS of Milan population aged 19 or older (N. 2,981,997), 74.74% of subjects (N. 2,228,915) were fully vaccinated and an additional 9.63% (N. 287,253) were subjects who, as of 30 September 2021, had received a single vaccine dose. Instead, 15.62% of the population (N. 465.829) was not vaccinated. The descriptive characteristics of the population with respect to vaccination outcome are reported in Table 1.

STUDY 2: ANALYSIS OF PREDICTIVE FACTORS ASSOCIATED WITH VACCINATION ADHERENCE

Table 2 reports the odds ratio estimates regarding failure to be vaccinated, obtained comparing fully vaccinated (double-jabbed) subjects with subjects who did not receive any dose, both in the population cohort as a whole and in subjects 50 years of age and older. Women are less likely to get vaccinated than men (OR 1.02; 95%CI 1.02-1.03). The younger age class (<40), taken as reference, is the one with the highest vaccine adherence, whereas vaccine hesitancy is most observed in the 50-59-year-old (OR 1.15; 95%CI 1.14-1.16) and 70+-year-old (OR 1.17; 95%CI 1.16-1.18) age groups. With respect to the deprivation index, failure to be vaccinated gradually increases from wealthier neighbourhoods to more deprived ones, and is at its highest in residents of severely deprived areas (OR 1.39; 95%CI 1.38-1.41). Lack of adherence is also more widespread in people who do not have Italian nationality, (OR 2.06; 95%CI 2.05-2.08) and progressively decreases with the increase in the number of comorbidities, although it rises in subjects with four or more diseases (OR 0.51; 95%CI 0.50-0.52). Finally, having had COVID-19 in the past is associated with a lower probability of not getting vaccinated (OR 0.71; 95%CI 0.69-0.72). The analysis of subjects aged 50 and over shows a greater tendency of women not to get vaccinated (OR 1.22; 95%CI 1.21-1.23) and a more intense effect of age on failure to be vaccinated (70+: OR 1.50; 95%CI 1.48-1.52). Compared to the entire cohort, in subjects over 50 nationality plays a slightly more important role (OR 2.27; 95%CI 2.24-2.31), while the effect of existing comorbidities (4+: OR 0.70; 95%CI 0.68-0.71) and a previous COVID-19 diagnosis (OR 0.80; 95%CI 0.78-0.82) appears more limited. Finally, since it was possible to reconstruct the adherence to previous cancer screening and flu vaccine programmes for this segment of the population, it was possible to observe that a greater propensity toward prevention is associated with a marked reduction in

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CHARACTERISTICS	UNVACCINATED		ONE DOSE		TWO DOSES		TOTAL
	N.	%	N.	%	N.	%	N.
Gender							
Men	220,853	47.41	147,984	51.52	1,058,326	47.48	**1,427,163**
Women	244,976	52.59	139,269	48.48	1,170,589	52.52	**1,554,834**
Age group (years)							
<40	136,925	29.39	70,299	24.47	571,337	25.63	**778,561**
40-49	95,371	20.47	42,046	14.64	396,473	17.79	**533,890**
50-59	89,935	19.31	99,684	34.70	396,535	17.79	**586,154**
60-69	59,386	12.75	43,925	15.29	319,793	14.35	**423,104**
70+	84,212	18.08	31,299	10.90	544,777	24.44	**660,288**
Deprivation index							
Very affluent	73,939	15.87	49,561	17.25	427,899	19.20	**551,399**
Affluent	74,589	16.01	51,464	17.92	412,161	18.49	**538,214**
Average	78,012	16.75	52,671	18.34	410,312	18.41	**540,995**
Deprived	84,248	18.09	52,123	18.15	401,371	18.01	**537,742**
Severely deprived	105,569	22.66	53,948	18.78	391,012	17.54	**550,529**
Missing	49,472	10.62	27,486	9.57	186,160	8.35	**263,118**
Citizenship							
Italian	354,728	76.15	244,100	84.98	1,968,249	88.31	**2,567,077**
Foreign	111,101	23.85	43,153	15.02	260,666	11.69	**414,920**
Comorbidities							
None	337,039	72.35	196,269	68.33	1,295,784	58.14	**1,829,092**
1	64,117	13.76	50,287	17.51	416,401	18.68	**530,805**
2	28,772	6.18	20,721	7.21	225,620	10.12	**275,113**
3	15,884	3.41	9,953	3.46	134,406	6.03	**160,243**
4+	20,017	4.30	10,023	3.49	156,704	7.03	**186,744**
Total	**465,829**	**15.62**	**287,253**	**9.63**	**2,228,915**	**74.75**	**2,981,997**

Table 1. Characteristics of the ATS of Milan population eligible for vaccination ≥19 years of age, for vaccination outcome as of 30.09.2021.
Tabella 1. Caratteristiche della popolazione della ATS di Milano eleggibile alla vaccinazione ≥19 anni, per esito della vaccinazione al 30.09.2021.

the risk of failing to receive COVID-19 vaccination (OR 0.23; 95%CI 0.23-0.24), representing the strongest predictor of this analysis, leading to an increase in the AUC of the model from 0.61 to 0.74.

STUDY 3: VACCINATION EFFECTIVENESS IN THE FIELD (VACCINATED *VS* UNVACCINATED)

Over the study period, hospital admissions for COVID-19 in the unvaccinated population amounted to 5,672 (1.22%) compared to 1,013 in the fully vaccinated population (0.05%); deaths were 15,198 (4.51%) among the unvaccinated, compared to 8,733 in the vaccinated group (0.32%) (Table 3).
Table 3 also reports the estimates of the risk of hospitalization for COVID-19 and general mortality obtained comparing the fully vaccinated population with the unvaccinated population, stratified by chronic disease, using Cox models including the date of the second vaccination as time-dependent variable in the regression model. The estimates show that in fully vaccinated subjects the risk of hospitalization and mortality for COVID-19 is lower compared to unvaccinated subjects. These results can be observed in the total population (hospitalization HR 0.17; 95%CI 0.14-0.20; death HR 0.63; 95%CI 0.59-0.67), in the population with no medical conditions (hospitalization HR 0.25; 95%CI 0.17-0.38; death HR 0.54; 95%CI 0.38-0.75), and in every subgroup of chronic conditions, without exception.

STUDY 4: PREDICTIVE FACTORS FOR COVID-19 RELATED HOSPITALIZATION IN THE VACCINATED POPULATION

Focusing exclusively on the fully vaccinated population, Table 4 reports the estimated hospitalization risks with

CHARACTERISTICS	ENTIRE COHORT							AGE ≥ 50 YEARS						
	UNVACCINATED		TWO DOSES		TOTAL	OR	(95%CI)	UNVACCINATED		TWO DOSES		TOTAL	OR	(95%CI)
	N.	%	N.	%				N.	%	N.	%			
Gender														
Men	220,853	47.41	1,058,326	47.48	**1,279,179**	1	Reference	106,593	45.64	571,102	45.29	**677,695**	1	Reference
Women	244,976	52.59	1,170,589	52.52	**1,415,565**	1.02	(1.02-1.03)	126,940	54.36	690,003	54.71	**816,943**	1.22	(1.21-1.23)
Age group (years)														
<40	136,925	29.39	571,337	25.63	**708,262**	1	Reference							
40-49	95,371	20.47	396,473	17.79	**491,844**	1.06	(1.05-1.07)							
50-59	89,935	19.31	396,535	17.79	**486,470**	1.15	(1.14-1.16)	89,935	38.51	396,535	31.44	**486,470**	1	Reference
60-69	59,386	12.75	319,793	14.35	**379,179**	1.11	(1.10-1.13)	59,386	25.43	319,793	25.36	**379,179**	1.18	(1.17-1.20)
70+	84,212	18.08	544,777	24.44	**628,989**	1.17	(1.16-1.18)	84,212	36.06	544,777	43.20	**628,989**	1.50	(1.48-1.52)
Deprivation index														
Very affluent	73,939	15.87	427,899	19.20	**501,818**	1	Reference	40,971	17.54	264,610	20.98	**305,581**	1	Reference
Affluent	74,589	16.01	412,161	18.49	**486,750**	1.04	(1.02-1.05)	40,101	17.17	246,857	19.57	**286,958**	1.05	(1.03-1.07)
Average	78,012	16.75	410,312	18.41	**488,324**	1.07	(1.06-1.08)	41,143	17.62	244,372	19.38	**285,515**	1.07	(1.06-1.09)
Deprived	84,248	18.09	401,371	18.01	**485,619**	1.14	(1.13-1.16)	43,626	18.68	235,132	18.64	**278,758**	1.16	(1.14-1.18)
Severely deprived	105,569	22.66	391,012	17.54	**496,671**	1.39	(1.38-1.41)	54,425	23.31	227,700	18.06	**282,125**	1.40	(1.38-1.42)
Missing	49,472	10.62	186,160	8.35	**235,632**	1.12	(1.10-1.13)	13,267	5.68	42,434	3.36	**55,701**	1.13	(1.10-1.16)
Citizenship														
Italian	354,728	76.15	1,968,249	88.31	**2,322,977**	1	Reference	193,781	82.98	1,183,415	93.84	**1,377,196**	1	Reference
Foreign	111,101	23.85	260,666	11.69	**371,767**	2.06	(2.05-2.08)	39,752	17.02	77,690	6.16	**117,442**	2.27	(2.24-2.31)
Comorbidity														
None	337,039	72.35	1,295,784	58.14	**1,632,823**	1	Reference	131,189	56.18	476,851	37.81	**608,040**	1	Reference
1	64,117	13.76	416,401	18.68	**480,518**	0.60	(0.60-0.61)	44,192	18.92	306,972	24.34	**351,164**	0.63	(0.63-0.64)
2	28,772	6.18	225,620	10.12	**254,392**	0.50	(0.50-0.51)	24,236	10.38	198,591	15.75	**222,827**	0.59	(0.58-0.60)
3	15,884	3.41	134,406	6.03	**150,290**	0.47	(0.46-0.48)	14,500	6.21	125,950	9.99	**140,450**	0.59	(0.58-0.60)
4+	20,017	4.30	156,704	7.03	**176,721**	0.51	(0.50-0.52)	19,416	8.31	152,741	12.11	**172,157**	0.70	(0.68-0.71)
COVID-19 diagnosis														
No	452,242	97.08	2,125,993	95.38	**2,578,235**	1	Reference	226,208	96.86	1,215,092	96.35	**1,441,300**	1	Reference
Yes	13,587	2.92	102,922	4.62	**116,509**	0.71	(0.69-0.72)	7,325	3.14	46,013	3.65	**53,338**	0.80	(0.78-0.82)
Prevention Propensity														
No								171,842	73.58	484,373	38.41	**65,6215**	1	Reference
Yes								61,691	26.42	776,732	61.59	**83,8423**	0.23	(0.23-0.24)
Total	**465,829**		**2,228,915**		**2,294,744**			**233,533**		**1,261,105**		**1,494,638**		

Table 2. Distribution of a number of sociodemographic variables, odds ratio (OR) and corresponding 95% confidence interval (95% CI), estimated using a multivariate unconditional logistic model to assess the predictors associated with failure to be vaccinated.
Tabella 2. Distribuzione di alcune variabili sociodemografiche, *odds ratio* (OR) e corrispondenti intervalli di confidenza al 95% (IC 95%) stimati mediante un modello logistico non condizionato multivariato per la valutazione dei predittori associati al mancato accesso alla vaccinazione.

respect to the previously analysed sociodemographic characteristics. The risk of hospitalization among vaccinated subjects does not differ by gender (HR 0.99; 95%CI 0.88-1.11), while with respect to age, in every age group a higher risk of hospitalization can be observed compared to the reference class (<40), especially for the older age groups (60-69: HR 1,50; 95%CI 1.02-2.21 and 70+: HR 5.02; 95%CI 3.55-7.10). With respect to the deprivation index, a clear gradient emerges, with the risk of hospitalization gradually increasing as one goes from subjects living in more affluent neighbourhoods to those living in more deprived neighbourhoods, until the risk is almost double when comparing the two extreme categories (HR 1.88; 95%CI 1.57-2.25). Vaccinated subjects of foreign nationality show a hospitalization risk which is almost double compared to vaccinated Italian subjects (HR 1.78; 95%CI 1.33-2.36). Among vaccinated subjects, having at least one chronic disease was associated with a greater risk of hospitalization compared to not having any medical condition, and the risk tends to increase with the number of chronic conditions. Finally, subjects with a previous COVID-19 diagnosis show a risk of hospitalization for COVID-19 following vaccination comparable to subjects who did not previously have the disease (HR 1.13; 95%CI 0.88-1.46).

For the fully vaccinated population, Table 5 reports the estimates of hospitalization risk with respect to individual chronic conditions, adjusted for gender, age, deprivation index, nationality, number of comorbidities, and previous COVID-19 infection. With the exception of high blood

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pressure, whose presence in vaccinated subjects is associated with a lower risk of hospitalization (HR 0.77; 95%CI 0.66-0.90), the presence of a medical condition is associated with a higher risk of hospitalization, with statistically significant coefficients for all chronic conditions except chronic bowel disease (HR 1.01; 95%CI 0.60-1.72), heart disease (HR 1.14; 95%CI 0.99-1.33) and autoimmune disorders (HR 1.09; 95%CI 0.76-1.57). Specifically, the highest hazard ratios are observed in subjects with heart failure (HR 2.12; 95%CI 1.80-2.49), immunocompromised patients (HR 2.02; 95%CI 1.51-2.69), and transplant recipients (HR 1.85; 95%CI 1.11-3.29).

DISCUSSION

The study primarily highlights the potentiality of using available health information systems, and organically presents an assessment that examines many aspects, including a description of the population according to vaccine adherence, a characterization of the unvaccinated population, the effectiveness of the vaccine campaign in terms of COVID-19-related hospitalization and all-cause death, and identification of the characteristics of fully vaccinated subjects presenting with subsequent hospitalization outcomes.

This evaluation was useful to gauge the impact of the introduction of COVID-19 vaccination in the area covered by the ATS of Milan, especially considering the size of the population served and the peculiarity of an area in which COVID-19 registered a high incidence and in which vaccine adherence is high. The evaluation of vaccine effectiveness reports data extremely similar to those found in international studies in the literature[34,35] and ISS computations conducted in Italy,[24] and makes it possible to validate the results of the randomized clinical trials in a general population and in real data.[4-10]

STUDIES 1 AND 2: DESCRIPTION OF VACCINE ADHERENCE AND PREDICTIVE FACTORS OF VACCINATION

In the area covered by the ATS of Milan, high adherence to vaccination (at least one dose of vaccine) is recorded, comparable to the data reported for Lombardy Region.[36] As has been observed in other studies,[10,37-39] the unvaccinated population has a different sociodemographic distribution compared to the vaccinated population. To date, the factors that characterize the population that fails to get vaccinated have not been greatly investigated in the literature:[38] population data are scarce, and usually

CHRONIC CONDITIONS	N. HOSPITALIZED / N. UNVACCINATED	N. HOSPITALIZED / N. VACCINATED	HR#	(95%CI)	N. DECEASED / N. UNVACCINATED	N. DECEASED / N. VACCINATED	HR#	(IC95%)
Immunocompromised patients	214/3,744	39/19,568	**0.09**	**(0.03-0.30)**	1,865/3,744	973/19,568	**0.22**	**(0.18-0.29)**
Transplant recipients	36/718	12/4,990	**0.16**	**(0.02-1.46)**	123/718	52/4,990	**0.09**	**(0.03-0.25)**
Chronic kidney failure/Dialysis	343/3,821	74/23,758	**0.21**	**(0.10-0.42)**	1,208/3,821	711/23,758	**0.42**	**(0.33-0.53)**
Chronic obstructive pulmonary disease	687/13,276	167/87,517	**0.27**	**(0.17-0.43)**	2,372/13,276	1237/87,517	**0.31**	**(0.26-0.38)**
Neurological disorders	392/4,604	77/25,686	**0.09**	**(0.05-0.17)**	1,707/4,604	1109/25,686	**0.27**	**(0.23-0.32)**
Cirrhosis	99/1,549	18/7,927	**0.17**	**(0.04-0.72)**	372/1,549	153/7,927	**0.40**	**(0.24-0.68)**
Chronic bowel disease	57/2,071	13/15,368	**0.04**	**(0.01-0.25)**	125/2,071	57/15,368	**0.22**	**(0.10-0.50)**
High blood pressure	2,929/65,117	696/557,496	**0.16**	**(0.13-0.20)**	9,876/65,117	5,859/557,496	**0.44**	**(0.41-0.48)**
Arterial vascular disease	271/3,486	57/21,989	**0.17**	**(0.08-0.39)**	1,026/3,486	553/21,989	**0.37**	**(0.28-0.48)**
Heart failure	832/7,718	196/43,177	**0.20**	**(0.13-0.31)**	3,054/7,718	1,589/43,177	**0.31**	**(0.27-0.37)**
Cerebral vascular disease	569/6,924	117/39,647	**0.16**	**(0.09-0.26)**	2,262/6,924	1,219/39,647	**0.43**	**(0.36-0.50)**
Heart disease	2,104/31,496	464/228,567	**0.16**	**(0.12-0.21)**	7,072/31,496	4,036/228,567	**0.41**	**(0.38-0.45)**
Autoimmune disorders	87/2,326	24/16,717	**0.25**	**(0.07-0.89)**	236/2,326	123/16,717	**0.64**	**(0.37-1.11)**
Diabetes	1,241/24,611	297/161,599	**0.18**	**(0.12-0.26)**	3,563/24,611	1981/161,599	**0.48**	**(0.41-0.55)**
No disease	1,485/337,039	115/1,295,784	**0.25**	**(0.17-0.38)**	1,495/337,039	839/1,295,784	**0.54**	**(0.38-0.75)**
Total	5,672/465,829	1,013/ 2,228,915	**0.17**	**(0.14-0.20)**	15,198/465,829	8,733/222,8915	**0.63**	**(0.59-0.67)**

NOTE: subjects with a single vaccine dose were excluded / ***NOTA:*** *sono stati esclusi i ricoveri precedenti ai 14 giorni nel gruppo dei vaccinati e i soggetti con una sola dose vaccinale.*
adjusted for gender, age, socioeconomic position, citizenship, number of comorbidities, COVID-19 infection in 2020 / *aggiustati per genere, età, stato socioeconomico, cittadinanza, numero di comorbidità, infezione COVID-19 nel 2020*

Table 3. Hazard ratio (HR) for hospitalization for COVID-19 (hospital admissions occurring prior to 14 days after second dose in vaccinated subjects were excluded) and all-cause mortality among vaccinated and unvaccinated and corresponding 95% confidence intervals, estimated using Cox models that consider a single medical condition at a time.
Tabella 3. *Hazard ratio (*HR) per ricovero ospedaliero per COVID-19 e mortalità per tutte le cause tra vaccinati e non vaccinati e corrispondenti intervalli di confidenza al 95% stimati mediante modelli di Cox che considerano la singola patologia alla volta.

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SOCIODEMOGRAPHIC CHARACTERISTICS	COVID-19 HOSPITALIZATIONS						HR	(95%CI)
	NO		YES		TOTALE			
	N.	%	N.	%	N.	%		
Gender								
Man	1,057,781	47.48	545	45.68	1,058,326	47.48	1	Reference
Women	1,169,941	52.52	648	54.32	1,170,589	52.52	0.98	(0.87-1.10)
Age group (years)								
<40	571,293	25.64	44	3.69	571,337	25.63	1	Reference
40-49	396,436	17.80	37	3.10	396,473	17.79	0.94	(0.61-1.46)
50-59	396,462	17.80	73	6.12	396,535	17.79	1.33	(0.90-1.96)
60-69	319,705	14.35	88	7.38	319,793	14.35	1.50	(1.02-2.21)
70+	543,826	24.41	951	79.72	544,777	24.44	5.02	(3.55-7.10)
Deprivation index								
Very affluent	427,707	19.20	192	16.09	427,899	19.20	1	Reference
Affluent	411,985	18.49	176	14.75	412,161	18.49	1.03	(0.84-1.27)
Average	410,114	18.41	198	16.60	410,312	18.41	1.18	(0.96-1.43)
Deprived	401,099	18.00	272	22.80	401,371	18.01	1.64	(1.36-1.97)
Severely deprived	390,692	17.54	320	26.82	391,012	17.54	1.88	(1.57-2.25)
Missing	186,125	8.35	35	2.93	186,160	8.35	1.47	(1.02-2.13)
Citizenship								
Italian	1,967,113	88.3	1,136	95.22	1,968,249	88.31	1	Reference
Foreign	260,609	11.7	57	4.78	260,666	11.69	1.78	(1.34-2.36)
Comorbidities								
None	1,295,637	58.16	147	12.32	1,295,784	58.14	1	Reference
1	416,236	18.68	165	13.83	416,401	18.68	1.63	(1.29-2.07)
2	225,434	10.12	186	15.59	225,620	10.12	2.41	(1.89-3.06)
3	134,219	6.02	187	15.67	134,406	6.03	3.39	(2.65-4.32)
4+	156,196	7.01	508	42.58	156,704	7.03	6.66	(5.35-8.30)
COVID-19 diagnosis								
No	2,137,895	95.97	1,129	94.64	2,139,024	95.97	1	Reference
Yes	89,827	4.03	64	5.36	89,891	4.03	1.13	(0.88-1.46)
Total	**2,225,768**		**1,193**		**2,226,961**			

Table 4. Distribution of certain specific sociodemographic characteristics in subjects who received two vaccine doses for COVID-19 related hospitalization. The table reports the hazard ratio (HR) for hospitalization and corresponding 95% confidence intervals estimated using Cox models that consider all variables in the table in a single multivariate model.
Tabella 4. Distribuzione per alcune specifiche caratteristiche sociodemografiche dei soggetti sottoposti a due dosi vaccinali, per ricovero per COVID-19. Vengono riportati gli *hazard ratio* (HR) di ricovero e i corrispondenti intervalli di confidenza al 95% stimati mediante modelli di Cox che considerano tutte le variabili presenti nella tabella in un unico modello multivariato.

come from countries such as the UK and USA, which are strongly characterized by multiethnicity and therefore focus strongly on the role of ethnicity.[40,41] The study carried out by the ATS of Milan points to the independent role of sociodemographic condition and nationality, confirming that vaccine programme adherence is strongly influenced by how information and communication permeates to the most deprived and marginal strata of the population. This evidence exactly reproduces the differences that exist between the Western world and the developing countries, underscores the need to implement global vaccination policies, and highlights how vaccination campaigns that are not able to include the entire population need to be rethought.[40,41]

Contrary to what is reported in the literature,[39,42] adherence in the younger age classes (<40) was greater than in the older age classes. This can be associated with the policies adopted by Italy, especially with respect to the most exposed workers (healthcare workers, teachers, etc.), the requirement of a vaccination pass (green pass) which was introduced during the summer months, as well as the formidable adherence by the younger population, a consequence of the rules for vacations/summer travel, and going back to school. Furthermore, the addition of data regarding the presence of comorbidities made it possible to obtain estimates adjusted for this component, which is absent in the other studies and strongly correlated to age. Even the greater adherence to vaccination

CHRONIC CONDITIONS	COVID1-9 HOSPITALIZATIONS						HR#	(95%CI)
	NO		YES		TOTALE			
	N.	%	N.	%	N.	%		
Immunocompromised patients								
Absent	2,208,203	99.12	1,144	95.89	2,209,347	99.12	1	Reference
Present	19,519	0.88	49	4.11	19,568	0.88	2.02	(1.52-2.69)
Transplant recipients								
Absent	2,222,745	99.78	1,180	98.91	2,223,925	99.78	1	Reference
Present	4,977	0.22	13	1.09	4,990	0.22	1.90	(1.09-3.29)
Chronic kidney failure / Dialysis								
Absent	2,204,055	98.94	1,102	92.37	2,205,157	98.93	1	Reference
Present	23,667	1.06	91	7.63	23,758	1.07	1.54	(1.23-1.92)
Chronic obstructive pulmonary disease								
Absent	2,140,397	96.08	1,001	83.91	2,141,398	96.07	1	Reference
Present	87,325	3.92	192	16.09	87,517	3.93	1.63	(1.39-1.92)
Neurological disorders								
Absent	2,202,128	98.85	1,101	92.29	2,203,229	98.85	1	Reference
Present	25,594	1.15	92	7.71	25,686	1.15	1.72	(1.39-2.14)
Cirrhosis								
Absent	2,219,817	99.65	1,171	98.16	2,220,988	99.64	1	Reference
Present	7,905	0.35	22	1.84	7,927	0.36	1.65	(1.08-2.52)
Chronic bowel disease								
Absent	2,212,368	99.31	1,179	98.83	2,213,547	99.31	1	Reference
Present	15,354	0.69	14	1.17	15,368	0.69	1.01	(0.60-1.72)
High blood pressure								
Absent	1,671,038	75.01	381	31.94	1,671,419	74.99	1	Reference
Present	556,684	24.99	812	68.06	557,496	25.01	0.77	(0.66-0.90)
Arterial vascular disease								
Absent	2,205,803	99.02	1,123	94.13	2,206,926	99.01	1	Reference
Present	21,919	0.98	70	5.87	21,989	0.99	1.28	(1.00-1.64)
Heart failure								
Absent	2,184,779	98.07	959	80.39	2,185,738	98.06	1	Reference
Present	42,943	1.93	234	19.61	43,177	1.94	2.12	(1.80-2.49)
Cerebral vascular disease								
Absent	2,188,214	98.23	1,054	88.35	2,189,268	98.22	1	Reference
Present	39,508	1.77	139	11.65	39,647	1.78	1.45	(1.21-1.75)
Heart disease								
Absent	1,999,691	89.76	657	55.07	2,000,348	89.75	1	Reference
Present	228,031	10.24	536	44.93	228,567	10.25	1.14	(0.99-1.32)
Autoimmune disorders								
Absent	2,211,036	99.25	1,162	97.40	2,212,198	99.25	1	Reference
Present	16,686	0.75	31	2.60	16,717	0.75	1.09	(0.76-1.57)
Diabetes								
Absent	2,066,467	92.76	849	71.17	2,067,316	92.75	1	Reference
Present	161,255	7.24	344	28.83	161,599	7.25	1.30	(1.13-1.49)
Total	**2,227,722**		**1,193**		**2,228,915**			

adjusted for gender, age, socioeconomic position, citizenship, number of comorbidities, COVID-19 infection in 2020 / *aggiustati per genere, età, stato socioeconomico, cittadinanza, numero di comorbidità, infezione COVID-19 nel 2020*

Table 5. Distribution of certain specific comorbidities in subjects who received two vaccine doses for COVID-19 related hospitalization. The table reports the hazard ratio (HR) for hospitalization and corresponding 95% confidence intervals, estimated using Cox models adjusted for all confounders reported in Table 4.
Tabella 5. Distribuzione di alcune specifiche comorbidità nei soggetti sottoposti a due dosi vaccinali per ricovero per COVID-19. Vengono riportati gli *hazard ratio* (HR) di ricovero e i corrispondenti intervalli di confidenza al 95% stimati mediante modelli di Cox corretto per tutti i confondenti riportati nella tabella 4.

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on the part of subjects with a previous COVID-19 infection goes against the tendency observed by others.[42] On the other hand, the lower adherence by women and the most disadvantaged strata of the population is confirmed.[39,42] The effect on women, which is particularly strong in the analysis on women over 50, is decidedly unexpected, as generally the female population participates in greater measure in health prevention and protection campaigns. However, it must not be forgotten that mass media insistently spread news about the higher frequency of thromboembolic side effects in females, and this might be one of the determinants of the lower adherence in women, and certainly deserves further study.
It was observed that subjects with comorbidities are more inclined to get vaccinated, but subjects with 4 or more comorbidities seem to have a lower vaccination adherence. This could be linked to a clinical status that is a contraindication to vaccination, severe frailness, terminal chronic illness, or difficulty in taking part in the vaccination campaign.

STUDY 3: EFFECTIVENESS OF VACCINATION IN THE POPULATION (VACCINATED *VS* UNVACCINATED)

The evidence observed with respect to vaccine effectiveness reaffirms the relevance of the factors that influence vaccination adherence. The estimates obtained for the entire population, corrected for potential confounders, are decidedly realistic and close to the estimates produced by the randomized trials.[4-10] The approach employed, with observation starting for vaccinated and unvaccinated subjects alike from January 1st, makes it possible to take into account the various stages of the epidemic and the different protection of vaccination on the spread of the virus (herd effect), so that it is the same at the time of hospitalization for vaccinated and unvaccinated alike. Analysis of mortality confirms[24,35] that vaccinated subjects are protected even with respect to death, although cause-specific mortality cannot be considered for this analysis.

STUDY 4: PREDICTIVE FACTORS FOR COVID-19 RELATED HOSPITALIZATION IN THE VACCINATED POPULATION

In the current scenario, the evidence with respect to the conditions that increase the risk of hospitalization for COVID-19 in fully vaccinated subjects is surely the most interesting part of the study. A recent population-based study conducted in the United Kingdom on subjects who completed the vaccination cycle shows significant increases in the risk of major events (i.e., death and hospitalization) in immunocompromised patients and chemotherapy patients, transplant recipients, patients with HIV/AIDS, neurological disorders, or other chronic conditions.[43]
The study of the ATS of Milan found the same identical pattern of at-risk medical conditions, also showing a decrease in the protective effect of vaccination for the most deprived social strata. Possible explanations[25,44,45] can be sought in a lesser degree of attention to the rules of prevention, jobs that are particularly exposed to risk, greater use of public transport, and difficulty in accessing the healthcare system in the initial stages of the disease, which eventually leads to the need for hospitalization.

STRENGTHS AND LIMITATIONS OF THE STUDY

An important strong point of this study is the wealth of information that reaffirms the relevance of sociodemographic status and identification of chronic conditions with a system that has by now been well validated nationally. Furthermore, the inclusion of a population of about 3 million people makes it possible in itself to obtain informative, robust estimates even in a setting other than a randomized study, which would not be ethical in a public health context.
One of the limits of this study in its evaluation of effectiveness in the field is the focus on the comparison solely between subjects vaccinated with two doses in the period examined and unvaccinated subjects. This restriction, which resulted in the exclusion of about 44% of the observed hospitalizations, made it possible, however, to analyse a more homogeneous population, since failure to get vaccinated with the second dose may be linked to diverse factors, such as:
1. onset of diseases or conditions that entail a contraindication to vaccination;
2. personal changes in the propensity to take part in the vaccine campaign;
3. a delay in administration, or failed administration of the second dose due to having contracted COVID-19 in the period between the two doses;
4. censor of subjects who received their first dose in the month of September 2021.
Another limitation is that, although a specific analysis for mortality was conducted, no analyses were carried out for competitive risks between hospitalization and death. Furthermore, having considered all causes of death, a selection bias may have been introduced, so that subjects more at risk of death due to terminal illness did not take up the vaccine campaign due to their conditions. Lack of update in the cohort of subjects who emigrated to places outside the area covered by the ATS of Milan, on the other hand, is negligible, as it accounts for about 1% of the population recruited on 1 January.

CONCLUSIONS

Although with all the limitations deriving from the use of an integrated system based on the available information

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sources and sources specifically organized to evaluate the epidemic trends, this study makes it possible to identify the characteristics of the population most at risk, on which it is necessary to take action in several ways, such as reinforcing messages concerning the need to maintain measures of protection and distancing in non-chronic deprived subjects, and identifying subjects with specific chronic conditions and advanced age that are eligible for the recently introduced booster dose.[1]

An additional dose, in a world in which developing countries have no access to vaccination, raises issues regarding correct identification of the target population; there is also need for numerous population-based studies, even carried out with different methods, in order to increase the healthcare systems' capacity to focus on the population that can benefit most, not wasting doses which must be used first of all to engage the unvaccinated population groups and second to activate systems of conveyance of doses to nations that have not yet reached a vaccine coverage sufficient to contain the epidemic.

Finally, an undoubtedly intriguing topic is the need to rethink both surveillance systems aimed to identifying variants, and population systems that will immediately capture a shift of the virus that provides it with an advantage in bypassing the immunity acquired through vaccination. In such a diverse evolving global scenario, to continue to use the same vaccine that was studied based on the viral variant of the first wave could be a problematic issue. For the future, therefore, coordination of national healthcare systems with vaccine producers is crucial, as the pharmaceutical industry needs to modify the vaccines producing mRNA components adapted to the various variants. It is necessary to consider the creation of national surveillance systems and guarantee systems that will safeguard nations in the relations with the pharmaceutical industry, in order not to lose the advantage that has been reached so far over an epidemic that will soon have been going on for two years, and has caused 5 million known deaths, but many more than that if one considers unreported deaths and deaths indirectly linked to the epidemic due to a reduction in hospital access and healthcare in general, including secondary prevention campaigns.

Conflicts of interest: none declared.

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