Boosters and time since last anti-COVID-19 vaccine dose: lead public health choices by real-time epidemiological assessment

Booster e distanza dall'ultima dose vaccinale anti-COVID-19: la valutazione epidemiologica continua per orientare le scelte di sanità pubblica

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WHAT IS ALREADY KNOWN

- **The level of anti-SARS-CoV-2 antibodies after the second vaccine dose peaks between 2 and 4 weeks after vaccination, decreasing in subsequent months with different trends depending on patient age, clinical conditions, and type of vaccine received.**
- **Results in the literature to date show that a third dose of vaccine reduces the COVID-19 infection rate by about 10 times, and the rate of severe disease or death by about 20 times, increasing the effectiveness of the vaccine in preventing hospitalization for COVID-19 by 93%, a severe course of the disease by 92%, and COVID-19 death by 81%.**

WHAT THIS STUDY ADDS

- **This population-based study, carried out on about 3 million people, confirms the effectiveness of a booster dose in preventing symptomatic disease and reducing COVID-19 hospitalization, COVID-19 intensive care admission, and death.**
- **The unvaccinated population is mainly comprised of subjects with few comorbidities, living in more deprived metropolitan areas, and in greater prevalence foreign.**
- **Unvaccinated subjects, compared to those who received a booster, have a 2-fold greater risk of symptomatic disease, a 10-fold greater risk of being hospitalized, a 9-fold greater risk of being admitted to intensive care, and a 3-fold greater risk of dying.**
- **A booster dose is urgently needed in subjects who received a second dose earlier, as they appear to be selected because of their older age, significant burden of chronic conditions, and greater deprivation.**

ABSTRACT

BACKGROUND: the levels of anti-SARS-CoV-2 antibodies after the second vaccine dose decline in the following months; an additional vaccine dose (booster) is able to swiftly restore the immune system, significantly reducing the risk of severe disease. In the winter of 2021, a new, particularly infectious variant made the need to increase booster coverage in the population even more urgent.

OBJECTIVES: to present, using real data, an evaluation of the effectiveness of the booster dose in reducing severe disease caused by SARS-CoV-2 infection in terms of COVID-19 hospitalization and intensive care admission, and all-cause mortality.

DESIGN: descriptive study of vaccination uptake; associative study of the factors linked with uptake of vaccination and COVID-19 symptoms; associative study of vaccine effectiveness against hospital admission and mortality.

SETTING AND PARTICIPANTS: population residing in the Milan and Lodi provinces (Lombardy Region, Northern Italy), eligible for anti-SARS-COV-2 vaccination, with subjects aged ≥19 years alive as at 01.10.2021, not residing in nursing homes, followed-up until 31.12.2021.

MAIN OUTCOME MEASURES: COVID-19 symptoms, hospitalization, intensive care hospitalization, and all-cause mortality in the period 01.10.2021-31.12.2021.

RESULTS: the cohort included 2,936,193 patients as of 01.10.2021; at the end of the observation period (31.12.2021), 378,616 (12.9%) were unvaccinated, 60,102 (2.0%) had received only 1 dose and had not had the disease, 68,777 (2.3%) had received only 1 dose and had had the disease, 412,227 (14.0%) were fully vaccinated with 2 doses less than 4 months earlier, 198,459 (6.8%) had received 2 doses [4,5) months earlier, 439,363 (15.0%) had received 2 doses [5,6) months earlier, 87,984 (3.0%) had received 2 doses [6,7) months earlier, 74,152 (2.5%) had received 2 doses more than 7 months earlier, 62,614 (2.1%) had received 2 doses and had had the disease, and, finally, 1,153,899 (39.3%) had received a booster shot. In the study period (01.10.2021-31.12.2021), characterized by a very high prevalence of the omicron variant, 121,620 cases (positive antigen/molecular test), 3,661 hospitalizations for COVID-19, 162 intensive care admissions for COVID-19, and 7,508 deaths from all causes were identified. Compared to unvaccinated subjects, subjects who received a booster had half the risk of being symptomatic, and had half the risk of experiencing fatigue, muscle aches, and dyspnoea. In comparison with boosted subjects, unvaccinated subjects had a 10-fold risk of hospitalization, a 9-fold risk of intensive care, and a 3-fold risk of dying.

CONCLUSIONS: this work highlights the effectiveness of vaccination in reducing serious adverse events in boosted subjects and the need to implement specific policies of engagement to bring subjects who received their second dose earliest to get a booster.

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

RIASSUNTO

INTRODUZIONE: è stato dimostrato che il livello di anticorpi anti-SARS-CoV-2 a seguito della seconda dose vaccinale declina nei mesi successivi e che la somministrazione di un'ulteriore dose vaccinale (*booster*) è in grado di ripristinare tempestivamente le difese immunitarie riducendo notevolmente il rischio di un decorso grave della malattia. Nell'inverno 2021, la circolazione di una nuova variante particolarmente diffusiva ha reso ancora più urgente l'implementazione della copertura della popolazione con la dose *booster*.

OBIETTIVI: valutare, tramite l'utilizzo di *real data*, l'efficacia della dose *booster* nel ridurre gli esiti riconducibili all'infezione da SARS-CoV-2 e il decorso grave della malattia in termini di ricoveri per COVID-19 ordinari e in terapia intensiva e di decesso per tutte le cause.

DISEGNO: studio descrittivo sui determinanti dell'adesione alla vaccinazione; studio associativo dell'adesione alla vaccinazione e sintomi riconducibili a COVID-19; studio associativo dell'efficacia della vaccinazione sul ridurre il rischio di ricoveri per COVID-19 e mortalità per tutte le cause.

SETTING E PARTECIPANTI: popolazione assistita e residente nelle province di Milano e Lodi, eleggibile alla vaccinazione anti-SARS-CoV-2, di età ≥19 anni e in vita al 01.10.2021, esclusi i residenti in RSA, seguita fino al 31.12.2021.

PRINCIPALI MISURE DI OUTCOME: sintomi riconducibili a COVID-19, ricoveri per COVID-19 ordinari e in terapia intensiva e decessi per tutte le cause nel periodo 01.10.2021-31.12.2021.

RISULTATI: dei 2.936.193 soggetti inclusi nella coorte al 01.10.2021, 378.616 (12,9%) al termine del periodo di osservazione (31.12.2021) non hanno effettuato nessun vaccino, 60.102 (2,0%) hanno 1 sola dose e non hanno avuto la malattia, 68.777 (2,3%) hanno 1 sola dose e hanno avuto la malattia, 412.227 (14,0%) hanno 2 dosi da meno di 4 mesi, 198.459 (6,8%) hanno 2 dosi da [4,5) mesi, 439.363 (15,0%) hanno 2 dosi da [5,6) mesi, 87.984 (3,0%) hanno 2 dosi da [6,7) mesi, 74.152 (2,5%) hanno 2 dosi da 7+ mesi, 62.614 (2,1%) hanno 2 dosi e hanno avuto la malattia e, infine, 1.153.899 (39,3%) hanno ricevuto il *booster*. Nel periodo di osservazione (01.10.2021-31.12.2021), durante il quale è risultata altamente prevalente la diffusione della variante omicron, sono stati identificati 121.620 casi (tampone antigenico/molecolare positivo), 3.661 ricoveri per COVID-19, 162 ricoveri per COVID-19 in terapia intensiva e 7.508 decessi per tutte le cause. Rispetto ai non vaccinati, i soggetti che avevano avuto la dose *booster* avevano il 50% di rischio in meno di essere sintomatici e avevano la metà del rischio di avere astenia, dolori muscolari e dispnea. I non vaccinati, rispetto a chi aveva fatto la dose *booster*, avevano un rischio maggiore di 10 volte di ricovero, di 9 volte di accesso alla terapia intensiva e di 3 volte di morte.

CONCLUSIONE: questo lavoro mette in luce l'effetto della vaccinazione nella riduzione degli eventi avversi gravi per chi si sottopone al *booster* e della necessità di implementare specifiche politiche di ingaggio per portare al *booster* i soggetti che hanno effettuato la seconda dose da più tempo.

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

INTRODUCTION

In Italy, the first confirmed diagnosis of COVID-19 infection was made in Codogno, a town located in the area covered by the ATS of Milan, in February 2020.[1-3] To date, more than 520,000 cases have been traced in the Metropolitan City of Milan, and about 12,000 excess deaths from all causes were detected in the two-year period 2020-2021 compared to the average of the years 2016-2019.[1]

In such an impactful situation, many efforts were made to orient possible actions that would mitigate the effects of the epidemic, starting with the development of protocols to identify the population most at risk with strategies relying on local healthcare services.[4] With the second wave, surveillance systems based on stratification models were developed to include the cases most at risk of unfavourable events in surveillance protocols, so that general practitioners would be alerted quickly in case of changes in symptoms.[5]

As vaccinations began in December 2020, assessments were made in order to develop the best strategy to differentiate access to the vaccine campaign based on risk.[4,6,7] With the activation of the vaccine campaign and intensification of phenomena of segregation with respect to vaccination offer, it was necessary to proceed both to an assessment of vaccine effectiveness on the field and to an identification of the sociodemographic characteristics of the non-uptaking population.[8] The assessment confirmed the effectiveness of vaccination in reducing both hospitalization and deaths, highlighting that unvaccinated subjects were prevalently represented – as in all public health actions aimed to the entire population – in the most deprived and frailer parts of the population, reaffirming an urgent need for tools that would increase their uptake, including going beyond the limits currently imposed by privacy laws.

The locally well-established Epidemiology Units were able to exploit health information systems at best, proving essential in providing evidence and continuous public health assessment. All this in a rapidly evolving context involving diverse needs, and acting with intelligence and adaptability even at such a particularly delicate time. Between October and December 2021, a new, particularly contagious variant began to circulate,[9] as, starting in October 2021, a third vaccine dose (booster) began to be offered[10] with priority being given to the population most at risk[10] – until, finally, vaccination became mandatory for everyone over 50 years of age.[11]

This followed evidence that the level of anti-SARS-CoV-2 antibodies after two vaccine doses peaks between 2 and 4 weeks after vaccination, decreasing in subsequent months with different trends depending on patient age, clinical conditions, and type of vaccine received.[12-14] On the other hand, a third dose of vaccine has been shown to be able to rapidly restore the immune system, significantly increasing anti-SARS-COV-2 antibodies compared to the second dose of vaccine.[13] According to data from Israel, one of the first nations to implement boosters, initially in high-risk subjects, a third dose reduces the COVID-19 infection rate by about 10 times and the rate of severe disease or death by about 20,[15] increasing the effectiveness of the vaccine in preventing hospitalization for COVID-19 by 93%, in preventing severe disease by 92%, and preventing death from COVID-19 by 81%.[16] Overall, data in the population regarding the duration of vaccine effectiveness are still conflicting.[17] A recent Italian study showed that in the Region of Lombardy, from the first to the ninth month after full vaccination, infection rates rose from 4.6 to 10.2, while severe disease rates rose from 1.0 to 1.7 every 10,000 months/person.[18]
Aim of this work is to present evidence based on real data with respect to:

- effectiveness of anti-SARS-CoV-2 vaccination, with particular focus on the effect of a booster dose in modifying symptoms at the onset of infection;
- effect of the combination between number of doses received, time since last vaccination, and/or previous SARS-COV-2 infection, with respect to three outcomes:

1. hospital admissions for COVID-19;
2. intensive care admissions for COVID-19;
3. general mortality.

The general aim of the study was to update the evidence already produced with respect to the assessment of the vaccine campaign in the phase preceding the introduction of boosters in the area covered by the Health Protection Agency of the Metropolitan City of Milan.[8] In light of the evidence that is accumulating in the literature, the main aim of this work was to evaluate, in a study with an extremely reduced time frame, the risks of unvaccinated cohorts or of subjects who received their last vaccine dose many months earlier, compared to subjects with a recent vaccination status (because they either received a booster dose or dose 2 less than 4 months before).

MATERIALS AND METHODS

The population included in the study has been described in a previous paper[8] and is comprised of the population residing in the Milan and Lodi provinces of Northern Italy, covered by ATS Milan, aged 19 or over and alive as of 01.01.2021.
From the population included in the previous study (2,981,997 subjects) we excluded deaths which had occurred up until 30.09.2021 and all nursing home residents, since the vaccine campaign was organized differently for this group compared to the rest of the population residing in the ATS area. Subjects were then followed up from inclusion in the study (residents of the area covered by ATS Milan alive as of 01.10.2021) up until the end of the observation on 31.12.2021.
Population data from the New Regional Office of Vital Statistics (Nuova Anagrafe Regionale - NAR) was integrated with the information from the permanent georeference system, developed and maintained by the Epidemiology Unit of ATS Milan, which made it possible to include information from the Population and Home Census of 2011, specifically, the deprivation index, calculated on the basis of the census tract.[19,20] 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 Lombardy Region.[21,22]
The personal data of the previous study was integrated with the vaccine data flow which records information concerning all doses (including boosters) received up until the end of the follow-up on 31.12.2021.
COVID-19 cases and their date of diagnosis were identified between 01.10.2021 and 31.12.2021 from the data flow of subjects who tested positive. This made it possible to position the vaccine history with respect to the disease of each patient in the cohort.
In order to meet the study objectives, the cohort was stratified in 10 levels, based on the combination of COVID-19 infection, number of vaccinations received, and time elapsed since last vaccination starting from 01.10.2021. Each subject can belong to just one of the classes thus identified:

- unvaccinated;
- vaccinated with a single dose;
- vaccinated with a single dose and SARS-COV-2 infection prior to vaccination;
- vaccinated with 2 doses received less than 4 months earlier;
- vaccinated with 2 doses [4,5) months earlier;
- vaccinated with 2 doses [5,6) months earlier;
- vaccinated with 2 doses [6,7) months earlier;
- vaccinated with 2 doses 7+ (≥7) months earlier;
- vaccinated with 2 doses and SARS-COV-2 infection prior to vaccination;
- those who received a booster dose.

The epidemiological surveillance systems of incident cases made it possible to identify asymptomatic subjects and collect information about symptoms at onset, i.e., the presence of the following specific COVID-19 symptoms: fever, headache, fatigue, muscle aches, respiratory

symptoms, dyspnoea, diarrhoea, conjunctivitis, loss of smell, loss of taste.[5]

Hospital admissions for COVID-19 during the three months of follow-up were identified integrating the hospital discharge database (HDD) updated to November 2021, using the specific COVID-19 codes, with the data provided by hospitals, which report all new COVID-19 hospitalizations with daily updates.

Vital status is updated periodically – with about a week's delay – by integrating municipal register data with patient registries.

Fully integrating data from all the described sources, using deterministic record linkage with an anonymized individual code, each patient was linked to information about their life status, and Intensive Care Unit (ICU) and non-ICU hospitalization as of 31.12.2021, occurring after vaccination during follow-up.

To evaluate the association between vaccination status and symptoms at disease onset in COVID-19 positive subjects, we used logistic regression models adjusted by gender, age, socioeconomic status, nationality, and number of comorbidities. The probability of the presentation of particular symptoms was separately modelled for each of the symptoms taken into account and odds ratios (ORs) and corresponding 95% confidence intervals were estimated.

Time at non-ICU hospitalization, intensive care admission, and death was instead modelled using multivariate Cox models adjusted by gender, age (included in 5-year age classes, and with the reference category comprised of all subjects under 50 years of age), socioeconomic status, nationality, and number of comorbidities, including the date of the last vaccination which occurred in the study period as dependent time variable. Effects were measured in terms of Hazard Ratio (HR) and corresponding 95% confidence intervals.

Finally, multiple correspondences were analysed to verify whether any association patterns were present between the qualitative variables in the study: comorbidities, symptoms, age, gender, number of vaccine doses and time since last vaccination (for details, see online supplementary materials).[23]

RESULTS

The previous study cohort[8] was made up of 2,981,997 subjects residing in the provinces of Milan and Lodi (in Northern Italy) aged ≥19 years alive as of 01.01.2021. From this database, 23,931 deaths which occurred until 30.09.2021 were excluded, along with 21,873 subjects residing in nursing homes up until 31.12.2021.

The new study cohort is therefore made up by 2,936,193 subjects whose characteristics at enrolment are described, for each vaccine group, in Table 1.

At enrolment, the cohort comprised 444,703 (15.1%) unvaccinated subjects, 179,719 subjects (6.1%) who received a single dose and had not had the disease, 99,943 subjects (3.4%) who received a single dose and had had the disease, 1,499,947 subjects (51.1%) who received 2 doses less than 4 months earlier, 310,847 subjects (10.6%) who received 2 doses [4,5) months earlier, 148,679 subjects (5.1%) who received 2 doses [5,6) months earlier, 90,043 subjects (3.1%) who received 2 doses [6,7) months earlier, 73,392 subjects (2.5%) who received 2 doses more than 7 months earlier, 88,920 subjects (3%) who received 2 doses and had had the disease. As expected, there are clear gradients with respect to vaccination status at enrolment, especially with regards to age and disease burden essentially linked to the inclusion policies of the vaccine campaign. It is clearly evident that the group of subjects vaccinated over 7 months earlier is prevalently comprised of healthcare workers; this group was immediately followed on a large scale by elderly people, and, finally, by the younger population, who gained access to the vaccine campaign later. Unvaccinated subjects are younger (31% under 40 years of age), with a greater prevalence of foreigners (27% of foreigners is unvaccinated compared to 14% of Italians), and with a lower disease burden.

Table 2 reports the transitions that occurred between enrolment and final status. In particular, out of 2,936,193 included subjects, at the end of the study period (31.12.2021), 378,616 (12.9%) had no vaccine, 60,102 (2.0%) had received a single dose and had not had the disease, 68,777 (2.3%) had received a single dose and had had the disease, 412,227 (14.0%) had received 2 doses less than 4 months earlier, 198,459 (6.8%) had received 2 doses less than [4,5) months earlier, 439,363 (15.0%) had received 2 doses less than [5,6) months earlier, 87,984 (3.0%) had received 2 doses less than [6,7) months earlier, 74,152 (2.5%) had received 2 doses more than 7 months earlier, 62,614 (2.1%) had received 2 doses and had had the disease, and, finally, 1,153,899 (39.3%) had received a booster dose.

Status change is most evident following the introduction of booster doses, as boosters represented the most relevant vaccination status change, essentially driven by regulations giving priority access to healthcare workers and frail elderly people, and then to the other population strata with a vaccination offer which in this phase did not limit access even in the absence of prior registration.

Considering the exclusions, during the three months of observation, 66,087 subjects (15%) who were unvaccinated as of 01.10.2021 had access to at least one dose of vaccine.

Table S1, which describes the cohort at the end of the period, including in the vaccination strata even the 7,508

CHARACTERISTICS	NOT VACCINATED		1 DOSE				2 DOSES												TOTAL	
			NO COVID-19		YES COVID-19		<4 MONTHS		[4-5) MONTHS		[5-6) MONTHS		[6-7) MONTHS		7+ MONTHS		YES COVID-19			
	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%
Gender																				
Men	210,508	47.3	95,275	53.0	49,023	49.1	744,568	49.6	142,357	45.8	61,207	41.2	35,401	39.3	27,288	37.2	43,525	48.9	**1,409,152**	**48.0**
Women	234,195	52.7	84,444	47.0	50,920	50.9	755,379	50.4	168,490	54.2	87,472	58.8	54,642	60.7	46,104	62.8	45,395	51.1	**1,527,041**	**52.0**
CAge class (years)																				
Mean - median (SD)	50,3-49,0 (17.8)		51,0-53,0 (14.2)		50,3-51,0 (16.4)		48,6-48,0 (16.3)		61,0-65,0 (15.5)		79,7-82,0 (12.5)		77,5-84,0 (17.5)		48,4-49,0 (14.5)		49,8-49,0 (17.4)		**52,9-52,0 (18.3)**	
[20,40)	135,335	30.4	40,490	22.5	27,878	27.9	480,296	32.0	35,718	11.5	4,057	2.7	5,780	6.4	21,564	29.4	27,065	30.4	**778,183**	**26.5**
[40,50)	94,397	21.2	22,429	12.5	18,679	18.7	323,075	21.5	33,093	10.6	3,726	2.5	3,703	4.1	15,396	21.0	18,714	21.0	**533,212**	**18.2**
[50,60)	88,580	19.9	74,626	41.5	24,116	24.1	293,520	19.6	52,135	16.8	5,172	3.5	5,439	6.0	20,629	28.1	20,221	22.7	**584,438**	**19.9**
[60,70)	57,079	12.8	27,556	15.3	15,698	15.7	206,452	13.8	82,761	26.6	4,442	3.0	4,761	5.3	11,187	15.2	9,959	11.2	**419,895**	**14.3**
70+	69,312	15.6	14,618	8.1	13,572	13.6	196,604	13.1	107,140	34.5	131,282	88.3	70,360	78.1	4,616	6.3	12,961	14.6	**620,465**	**21.1**
ASST																				
Milano	205,126	46.1	66,712	37.1	35,142	35.2	597,112	39.8	116,307	37.4	61,004	41.0	43,418	48.2	29,830	40.6	34,548	38.9	**1,189,199**	**40.5**
Rhodense	53,400	12.0	25,540	14.2	15,265	15.3	212,427	14.2	43,165	13.9	21,013	14.1	10,776	12.0	9,806	13.4	13,563	15.3	**404,955**	**13.8**
OVEST Milano	49,697	11.2	25,641	14.3	15,669	15.7	200,977	13.4	43,408	14.0	19,468	13.1	9,608	10.7	9,631	13.1	10,833	12.2	**384,932**	**13.1**
NORD Milano	33,944	7.6	13,070	7.3	8,646	8.7	113,113	7.5	23,408	7.5	12,347	8.3	7,650	8.5	5,601	7.6	8,781	9.9	**226,560**	**7.7**
Melegnano	76,541	17.2	36,804	20.5	19,327	19.3	271,269	18.1	63,312	20.4	25,588	17.2	13,125	14.6	13,390	18.2	15,895	17.9	**535,251**	**18.2**
Lodi	25,995	5.8	11,952	6.7	5,894	5.9	105,049	7.0	21,247	6.8	9,259	6.2	5,466	6.1	5,134	7.0	5,300	6.0	**195,296**	**6.7**
Deprivation index																				
Very affluent	70,058	15.8	30,116	16.8	18,031	18.0	272,876	18.2	64,816	20.9	34,356	23.1	21,986	24.4	14,924	20.3	15,955	17.9	**543,118**	**18.5**
Affluent	70,967	16.0	31,545	17.6	18,653	18.7	271,782	18.1	61,544	19.8	29,010	19.5	16,985	18.9	13,808	18.8	15,480	17.4	**529,774**	**18.0**
Aerage	74,295	16.7	32,316	18.0	19,078	19.1	272,461	18.2	60,593	19.5	28,203	19.0	16,055	17.8	13,386	18.2	16,283	18.3	**532,670**	**18.1**
Deprived	80,675	18.1	32,478	18.1	18,324	18.3	268,991	17.9	55,812	18.0	27,447	18.5	16,092	17.9	12,815	17.5	16,505	18.6	**529,139**	**18.0**
Severely deprived	101,470	22.8	34,333	19.1	18,236	18.2	264,139	17.6	52,580	16.9	25,819	17.4	16,107	17.9	10,792	14.7	17,258	19.4	**540,734**	**18.4**
Missing	47,238	10.6	18,931	10.5	7,621	7.6	149,698	10.0	15,502	5.0	3,844	2.6	2,818	3.1	7,667	10.4	7,439	8.4	**260,758**	**8.9**
Nationality																				
Italian	335,379	75.4	148,915	82.9	88,291	88.3	1,276,152	85.1	297,075	95.6	146,496	98.5	87,782	97.5	67,054	91.4	74,942	84.3	**2,522,086**	**85.9**
Foreign	109,324	24.6	30,804	17.1	11,652	11.7	223,795	14.9	13,772	4.4	2,183	1.5	2,261	2.5	6,338	8.6	13,978	15.7	**414,107**	**14.1**
Comorbiities																				
None	331,596	74.6	130,239	72.5	62,312	62.3	1,040,055	69.3	106,528	34.3	25,211	17.0	21,802	24.2	49,616	67.6	54,242	61.0	**1,821,601**	**62.0**
1	61,158	13.8	30,355	16.9	18,865	18.9	256,132	17.1	71,876	23.1	34,593	23.3	20,910	23.2	13,543	18.5	15,646	17.6	**523,078**	**17.8**
2	25,709	5.8	10,857	6.0	9,044	9.0	107,779	7.2	51,821	16.7	31,015	20.9	17,342	19.3	5,648	7.7	7,778	8.7	**266,993**	**9.1**
3	13,054	2.9	4,637	2.6	4,690	4.7	51,818	3.5	35,237	11.3	23,655	15.9	12,714	14.1	2,570	3.5	4,668	5.2	**153,043**	**5.2**
4+	13,186	3.0	3,631	2.0	5,032	5.0	44,163	2.9	45,385	14.6	34,205	23.0	17,275	19.2	2,015	2.7	6,586	7.4	**171,478**	**5.8**
TOTAL	**444,703**		**179,719**		**99,943**		**1,499,947**		**310,847**		**148,679**		**90,043**		**73,392**		**88,920**		2,936,193	

Table 1. Characteristics of the ATS Milan population over 19 years of age eligible for anti-COVID-19 vaccination, by vaccination status as of 01.10.2021.
Tabella 1. Caratteristiche della popolazione della ATS di Milano eleggibile alla vaccinazione anti-COVID-19 al di sopra dei 19 anni, per esito della vaccinazione al 01.10.2021.

(0.3%) deaths, reinforces what was observed at enrolment: a clear age effect is evident, with subjects who received 2 doses less than 4 months earlier being younger, whereas those who were vaccinated earliest with two doses or had already received a booster dose were older.
Table S1 compares the mean and median age of the various vaccination groups, highlighting that the median age of subjects vaccinated with 2 doses more than 7 months before is 8 years greater than boosted subjects and at least 10 years greater than the remaining classes. The previously described profile of unvaccinated subjects persists, with this group being made up of younger subjects, with few comorbidities, with a greater prevalence of foreigners, residing in more deprived metropolitan areas.
The characteristics in terms of disease burden as at 31.12.2021 are reported in table S2 where, in the group of subjects with time since vaccination greater than 7 months after the second dose, there is an evident greater frequency of serious chronic conditions, such as all cardiovascular diseases and diseases compromising the immune system, and the presence of a decreasing trend as the period of time since vaccination is reduced.
Overall, of the entire cohort – considering that the same period saw the occurrence of a fourth wave, with peaks of over 20,000 cases/day – 121,620 (4%) subjects contracted COVID-19 after inclusion in the study, but for 15,613 (12.8%) it was not possible to detect symptoms at onset, for a total of 106,007 cases with information about symptoms, the distribution of which by vaccination status is shown in table 3. There are evident differences in the proportion of cases that report various symptoms by vaccination category, with a clear trend for unvaccinated subjects, who overall notify symptoms (except for respiratory symptoms) in a greater proportion than vaccinated groups, while those vaccinated with two doses present decreasing frequency with the reduction of the time since their last dose. The same finding is present comparing the number of symptoms: 23% of unvaccinated patients and 20% of patients vaccinated with two doses more than 7 months earlier presents 4 or more symptoms, vs 8% of subjects who received a booster dose and 8% of subjects with two doses who developed the disease.
Table 4 reports the results of the logistic models that have as outcomes the presence of symptoms reported in table 3 and adjusted by gender, age, socioeconomic status, nationality, and number of comorbidities. Compared to unvaccinated subjects, subjects who received a booster had half the risk of being symptomatic or experiencing fatigue, muscle aches, and dyspnoea (the latter is the most severe symptom associated with infection and the major determinant in hospitalization).
In the study period (01.10.2021-31.12.2021), there were 3,661 non-ICU hospitalizations for COVID-19, 162 ICU admissions for COVID-19, and 7,508 deaths from all causes.
Real data evaluation of the effectiveness of the booster dose is presented in table 5, which also reports the gradients of estimated risks as a function of the time since last vaccination dose. Table S3 (see supplementary materials online) presents the estimates excluding from analysis the two groups of subjects vaccinated with 1 dose and 2 doses who had a COVID-19 diagnosis before their last vaccine dose, which are small groups characterized by few events, confirming the estimates presented in table 5. Boosted subjects were seen to have an HR of 0.10 for non-ICU hospitalization, 0.11 for ICU admission, and 0.33 for death compared to unvaccinated subjects. In terms of excess risk, it means unvaccinated subjects have a more than 10-fold risk of non-ICU hospitalization, a 9-fold risk of ICU admission, and a 3-fold risk of death. An excess risk for hospitalization and death also emerges clearly for those who received two doses of vaccine earlier and those who received a single dose and never had the disease, whereas protection against intensive care admission persists.

DISCUSSION

This study, which is based on extensive use of current healthcare databases, underlines three extremely topical points of discussion:
1. an effect of reduction in the risk of hospitalization for COVID-19, intensive care admission for COVID-19, and death for subjects who received a booster compared to unvaccinated subjects;
2. having received two doses and having been infected with COVID-19 confers in the short term a protection against hospitalization and intensive care admission comparable to a booster dose;
3. the unvaccinated population continues to show a disadvantage with respect to the risk of hospitalization, intensive care admission, and death.
The most original result of our study is that on a population level there is a clear association between risk of developing adverse events and time since last vaccine dose.
Having used as reference class the unvaccinated group, regardless of presence or absence of disease, makes the results of this study even more evident, showing a stable effectiveness of full vaccination that significantly weakens only when 7 or more months have elapsed since the last vaccination dose. Subjects whose last vaccination dose was received over 7 months before seem to belong to this category as a result of difficulties associated with age and chronic conditions rather than by choice,

VACCINATION STATUS AS OF 31.12.2021	VACCINATION STATUS AS OF 01.10.2021																			
		NOT VACCINATED		1 DOSE				2 DOSES												TOTAL	
				NO COVID-19		YES COVID-19		<4 MONTHS		[4-5) MONTHS		[5-6) MONTHS		[6-7) MONTHS		7+ MONTHS		YES COVID-19			
		N.	%	N.	%	N.	%	n.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%
	NOT vaccinated	378,616	85.1																	**378,616**	**12.9**
	1 single dose alone	18,155	4.1	41,947	23.3															**60,102**	**2.0**
	1 dose and COVID-19 before	10,245	2.3			58,532	58.6													**68,777**	**2.3**
	2 doses <4 months	35,513	8.0	104,336	58.1			272,378	18.2											**412,227**	**14.0**
	2 doses [4-5) months							198,459	13.2											**198,459**	**6.8**
	2 doses [5-6) months							439,363	29.3											**439,363**	**15.0**
	2 doses [6-7) months							87,984	5.9											**87,984**	**3.0**
	2 doses 7+ months							995	0.1	48,379	15.6	16,664	11.2	5,272	5.9	2,842	3.9			**74,152**	**2.5**
	2 doses and COVID-19 before	2,174	0.5	1,700	0.9	13,731	13.7											45,009	50.6	**62,614**	**2.1**
	Booster dose			31,736*	17.7	27,680*	27.7	500,768	33.4	262,468	84.4	132,015	88.8	84,771	94.1	70,550	96.1	43,911	49.4	**1,153,899**	**39.3**
	Total	**444,703**		**179,719**		**99,943**		**1,499,947**		**310,847**		**148,679**		**90,043**		**73,392**		**88,920**		**2,936,193**	

Table 2. Vaccination status at the start (01.10.2021) and at the end (31.12.2021) of the observation period of the population included in the study.
Tabella 2. Stato vaccinale all'inizio (01.10.2021) e alla fine (31.12.2021) del periodo di osservazione della popolazione della ATS di Milano inclusa nello studio.

* 26,348 subjects received the Johnson&Johnson vaccine: 24,771 1 single dose alone; 1,577 received 1 dose and had COVID before / *26.348 soggetti sono stati sottoposti al vaccino Johnson&Johnson: 24.771 1 dose - sola; 1.577 1 dose e COVID-19 prima*

SYMPTOMS	NOT VACCINATED		1 DOSE				2 DOSES												BOOSTER DOSE		TOTAL (N.)
			NO COVID-19		YES COVID-19		<4 MONTHS		[4-5) MONTHS		[5-6) MONTHS		[6-7) MONTHS		7+ MONTHS		YES COVID-19				
	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	
ASYMPTOMATIC *																					
No	11,406	74.8	3,270	71.5	7	41.2	6,451	67.9	7,876	69.7	24,301	71.6	6,648	74.0	5,081	73.5	23	37.1	9,020	58.2	**74,083**
Yes	3,846	25.2	1,301	28.5	10	58.8	3,044	32.1	3,419	30.3	9,620	28.4	2,337	26.0	1,832	26.5	39	62.9	6,476	41.8	**31,924**
FEVER *																					
Absent	8,901	58.4	3,036	66.4	13	76.5	6,845	72.1	8,008	70.9	23,270	68.6	6,020	67.0	4,432	64.1	51	82.3	12,847	82.9	**73,423**
Present	6,351	41.6	1,535	33.6	4	23.5	2,650	27.9	3,287	29.1	10,651	31.4	2,965	33.0	2,481	35.9	11	17.7	2,649	17.1	**32,584**
HEADACHE *																					
Absent	11,820	77.5	3,718	81.3	17	100.0	7,694	81.0	9,279	82.2	27,815	82.0	7,298	81.2	5,662	81.9	56	90.3	13,683	88.3	**87,042**
Present	3,432	22.5	853	18.7	0	0.0	1,801	19.0	2,016	17.8	6,106	18.0	1,687	18.8	1,251	18.1	6	9.7	1,813	11.7	**18,965**
FATIGUE *																					
Absent	10,142	66.5	3,278	71.7	14	82.4	6,996	73.7	8,405	74.4	25,020	73.8	6,405	71.3	4,853	70.2	54	87.1	12,555	81.0	**77,722**
Present	5,110	33.5	1,293	28.3	3	17.6	2,499	26.3	2,890	25.6	8,901	26.2	2,580	28.7	2,060	29.8	8	12.9	2,941	19.0	**28,285**
MUSCLE ACHES *																					
Absent	10,032	65.8	3,275	71.6	15	88.2	7,059	74.3	8,662	76.7	25,209	74.3	6,515	72.5	5,089	73.6	54	87.1	13,166	85.0	**79,076**
Present	5,220	34.2	1,296	28.4	2	11.8	2,436	25.7	2,633	23.3	8,712	25.7	2,470	27.5	1,824	26.4	8	12.9	2,330	15.0	**26,931**
RESPIRATORY SYMPTOMS *																					
Absent	6,970	45.7	1,918	42.0	11	64.7	4,043	42.6	4,493	39.8	13,413	39.5	3,444	38.3	2,725	39.4	43	69.4	7,614	49.1	**44,674**
Present	8,282	54.3	2,653	58.0	6	35.3	5,452	57.4	6,802	60.2	20,508	60.5	5,541	61.7	4,188	60.6	19	30.6	7,882	50.9	**61,333**
DYSPNOEA *																					
Absent	14,543	95.4	4,360	95.4	16	94.1	9,101	95.9	10,868	96.2	32,816	96.7	8,603	95.7	6,511	94.2	59	95.2	15,055	97.2	**101,932**
Present	709	4.6	211	4.6	1	5.9	394	4.1	427	3.8	1,105	3.3	382	4.3	402	5.8	3	4.8	441	2.8	**4,075**
DIARRHOEA *																					
Absent	13,752	90.2	4,274	93.5	15	88.2	8,907	93.8	10,731	95.0	32,126	94.7	8,431	93.8	6,458	93.4	60	96.8	14,949	96.5	**99,703**
Present	1,500	9.8	297	6.5	2	11.8	588	6.2	564	5.0	1,795	5.3	554	6.2	455	6.6	2	3.2	547	3.5	**6,304**
CONJUNCTIVITIS *																					
Absent	15,037	98.6	4,516	98.8	17	100.0	9,345	98.4	11,194	99.1	33,486	98.7	8,831	98.3	6,804	98.4	62	100.0	15,320	98.9	**104,612**
Present	215	1.4	55	1.2	0	0.0	150	1.6	101	0.9	435	1.3	154	1.7	109	1.6	0	0.0	176	1.1	**1,395**
ANOSMIA *																					
Absent	13,193	86.5	4,113	90.0	16	94.1	8,541	90.0	10,302	91.2	29,992	88.4	7,737	86.1	5,885	85.1	58	93.5	14,812	95.6	**94,649**
Present	2,059	13.5	458	10.0	1	5.9	954	10.0	993	8.8	3,929	11.6	1,248	13.9	1,028	14.9	4	6.5	684	4.4	**11,358**
AGEUSIA *																					
Absent	13,455	88.2	4,199	91.9	17	100.0	8,633	90.9	10,368	91.8	30,602	90.2	7,941	88.4	6,140	88.8	61	98.4	14,914	96.2	**96,330**
Present	1,797	11.8	372	8.1	0	0.0	862	9.1	927	8.2	3,319	9.8	1,044	11.6	773	11.2	1	1.6	582	3.8	**9,677**
TOTAL	**15,252**		**4,571**		**17**		**9,495**		**11,295**		**33,921**		**8,985**		**6,913**		**62**		**15,496**		**106,007**

Follows ▶

SYMPTOMS	NOT VACCINATED		1 DOSE				2 DOSES												BOOSTER DOSE		TOTAL (N.)
			NO COVID-19		YES COVID-19		<4 MONTHS		[4-5) MONTHS		[5-6) MONTHS		[6-7) MONTHS		7+ MONTHS		YES COVID-19				
	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	
NUMBER OF SYMPTOMS **																					
Asymptomatic	3,846	22.1	1,301	23.9	10	47.6	3,044	27.3	3,419	26.6	9,620	25.2	2,337	23.4	1,832	22.7	39	41.9	6,476	35.3	**31,924**
1	2,337	13.4	850	15.6	3	14.3	1,783	16.0	2,262	17.6	6,663	17.5	1,713	17.1	1,262	15.6	5	5.4	3,596	19.6	**20,474**
2	2,700	15.5	815	15.0	1	4.8	1,566	14.0	2,084	16.2	6,246	16.4	1,676	16.7	1,263	15.6	8	8.6	2,409	13.1	**18,768**
3	2,451	14.1	705	13.0	0	0.0	1,284	11.5	1,586	12.3	4,903	12.8	1,330	13.3	951	11.8	3	3.2	1,508	8.2	**14,721**
4+	3,918	22.5	900	16.5	3	14.3	1,818	16.3	1,944	15.1	6,489	17.0	1,929	19.3	1,605	19.9	7	7.5	1,507	8.2	**20,120**
Missing	2,157	12.4	871	16.0	4	19.0	1,656	14.9	1,582	12.3	4,259	11.2	1,023	10.2	1,171	14.5	31	33.3	2,859	15.6	**15,613**

Table 3. Symptoms at onset in COVID-19 patients over 19 years of age, by vaccination status.
Tabella 3. Sintomi all'esordio nei pazienti con COVID-19, per stato vaccinale nella popolazione al di sopra dei 19 anni.

* % refers to reportedly symptomatic subjects / *% si riferisce ai soggetti con sintomi rilevati*
** % refers to all subjects with known COVID-19 infection, including asymptomatic subjects / *% si riferisce a tutti i soggetti con infezione COVID-19 nota includendo anche i soggetti con sintomi mancanti*

SYMPTOMS	NOT VACCINATED	1 DOSE		2 DOSES						BOOSTER DOSE
		NO COVID-19	YES COVID-19	<4 MONTHS	[4-5) MONTHS	[5-6) MONTHS	[6-7) MONTHS	7+ MONTHS	YES COVID-19	
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Asymptomatic	Reference	1.16 (1.07-1.25)	3.93 (1.48-10.40)	1.43 (1.35-1.51)	1.29 (1.22-1.36)	1.17 (1.12-1.22)	1.07 (1.01-1.14)	1.01 (0.95-1.08)	4.98 (2.96-8.38)	2.09 (1.99-2.20)
Fever		0.72 (0.67-0.77)	0.45 (0.15-1.37)	0.55 (0.52-0.58)	0.59 (0.56-0.62)	0.64 (0.61-0.67)	0.68 (0.64-0.72)	0.77 (0.72-0.82)	0.31 (0.16-0.59)	0.29 (0.27 -0.30)
Headache		0.82 (0.75-0.89)		0.75 (0.70-0.80)	0.71 (0.67-0.76)	0.77 (0.73-0.81)	0.81 (0.75-0.86)	0.91 (0.84 -0.98)	0.37 (0.16-0.86)	0.50 (0.47-0.53)
Fatigue		0.80 (0.75-0.86)	0.46 (0.13-1.60)	0.69 (0.65-0.73)	0.68 (0.65-0.72)	0.71 (0.68-0.74)	0.78 (0.74-0.83)	0.88 (0.82-0.94)	0.30 (0.14-0.62)	0.48 (0.45-0.50)
Muscle Aches		0.78 (0.73-0.84)	0.26 (0.06-1.16)	0.65 (0.61-0.69)	0.60 (0.56-0.63)	0.67 (0.64-0.70)	0.73 (0.68-0.77)	0.76 (0.71-0.81)	0.29 (0.14 -0.60)	0.36 (0.34-0.38)
Respiratory symptoms		1.18 (1.11-1.27)	0.48 (0.18-1.32)	1.10 (1.05-1.16)	1.25 (1.19-1.31)	1.30 (1.25-1.35)	1.34 (1.26-1.41)	1.40 (1.31-1.48)	0.38 (0.22-0.65)	0.90 (0.86-0.94)
Dyspnoea		1.04 (0.88-1.21)	1.35 (0.18-10.30)	0.89 (0.78-1.01)	0.82 (0.72-0.93)	0.72 (0.65-0.79)	0.83 (0.73-0.95)	1.02 (0.89 -1.16)	1.05 (0.33-3.36)	0.56 (0.49-0.63)
Diarrhoea		0.66 (0.58-0.75)	1.32 (0.30-5.83)	0.60 (0.54-0.66)	0.49 (0.44-0.54)	0.52 (0.48-0.56)	0.57 (0.52-0.64)	0.64 (0.57-0.72)	0.31 (0.08-1.29)	0.34 (0.31-0.37)
Conjunctivitis		0.86 (0.64-1.17)		1.19 (0.97-1.47)	0.75 (0.59-0.96)	0.94 (0.80-1.11)	1.14 (0.92-1.41)	1.17 (0.93-1.49)		0.82 (0.67-1.01)
Anosmia		0.74 (0.67-0.83)	0.42 (0.06-3.17)	0.68 (0.62-0.73)	0.59 (0.54-0.64)	0.83 (0.79-0.88)	1.07 (0.99-1.15)	1.35 (1.24-1.47)	0.46 (0.17-1.26)	0.32 (0.29-0.35)
Ageusia		0.69 (0.62-0.78)		0.70 (0.64-0.76)	0.63 (0.58-0.69)	0.81 (0.76-0.86)	1.00 (0.92-1.09)	1.12 (1.03-1.23)	0.13 (0.02-0.92)	0.32 (0.29-0.35)

Table 4. Odds ratio# (OR) and corresponding 95% confidence intervals (95%CI) for the presence of symptoms at onset in patients over 19 years of age with COVID-19, by vaccination status^ as of 31.12.2021. Reference category: NOT vaccinated.
Tabella 4. Odds ratio# (OR) della presenza di sintomi all'esordio nei pazienti con COVID-19 e corrispondenti intervalli di confidenza al 95% (IC95%) per stato vaccinale^ al 31.12.2021 nella popolazione al di sopra dei 19 anni. Categoria di riferimento: NON vaccinati.

logistic model adjusted by gender, age, socioeconomic status, nationality (Italian vs. foreign) and number of comorbidities / *modelli logistici aggiustati per genere, età, stato socio economico, cittadinanza (Italiana vs straniera) e numero di comorbidità*
^ vaccination statuses highlighted in grey have been excluded from the model / *gli strati con le modalità dello stato vaccinale evidenziati in grigio sono stati esclusi dal modello*

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	HOSPITALIZED FOR COVID-19 / TOTAL	HR* (95%CI)	ICU FOR COVID-19 / TOTAL	HR* (95%CI)	DEATHS / TOTAL	HR* (95%CI)
NOT vaccinated	*1,111/378,616*	**Reference**	*91/378,616*	**Reference**	*1,223/378,616*	**Reference**
1 single dose alone	*208/60,102*	1.34 (1.15-1.56)	*4/60,102*	0.28 (0.10-0.76)	*208/60,102*	1.80 (1.56-2.09)
1 dose and COVID-19	*13/68,777*	0.07 (0.04-0.12)	*0/68,777*		*142/68,777*	0.98 (0.82-1.16)
2 doses <4 months	*168/412,227*	0.19 (0.16-0.22)	*2/412,227*	0.03 (0.01-0.12)	*159/412,227*	0.31 (0.26-0.36)
2 doses [4-5) months	*60/198,459*	0.18 (0.14-0.24)	*1/198,459*	0.05 (0.01-0.33)	*72/198,459*	0.53 (0.42-0.68)
2 doses [5-6) months	*463/439,363*	0.41 (0.37-0.46)	*24/439,363*	0.19 (0.12-0.29)	*453/439,363*	0.57 (0.51-0.64)
2 doses [6-7) months	*244/87,984*	0.73 (0.63-0.84)	*10/87,984*	0.25 (0.13-0.49)	*471/87,984*	1.47 (1.31-1.64)
2 doses 7+ months	*886/74,152*	1.65 (1.50-1.82)	*19/74,152*	0.57 (0.34-0.96)	*3612/74,152*	3.77 (3.52-4.03)
2 doses e COVID-19	*23/62,614*	0.12 (0.08-0.19)	*1/62,614*	0.08 (0.01-0.54)	*193/62,614*	1.14 (0.96-1.36)
Booster dose	*485/1,153,899*	0.10 (0.08-0.12)	*10/1,153,899*	0.11 (0.03-0.35)	*975/1,153,899*	0.33 (0.29-0.37)
TOTAL	***3,661/2,936,193***		***162/2,936,193***		***7,508/2,936,193***	

Table 5. Hazard ratio# (HR) and 95% confidence intervals (95%CI) for COVID-19-hospitalisation, COVID-19 admission to intensive care and death for all causes by vaccination status^ as of 31.12.2021 for the population over 19 years of age.
Tabella 5. Hazard ratio# (HR) e corrispondenti intervalli di confidenza al 95% (IC95%) di ricovero per COVID-19, accesso per COVID-19 in terapia intensiva (TI) e decesso per stato vaccinale^ al 31.12.2021 nella popolazione al di sopra dei 19 anni.

time-dependent models adjusted by gender, age (included in five-year classes), socioeconomic status, nationality (Italian vs. foreign), number of comorbidities, and date of last dose during the period 01.10.2021-31.12.2021 as time-dependent variable / *modelli tempo-dipendenti aggiustati per genere, età in classi quinquennali, stato socio economico, cittadinanza (Italiana vs straniera) e numero di comorbidità e con l'ultima vaccinazione effettuata nel periodo 01/10/2021-31/12/2021 come variabile tempo dipendente*
^ vaccination statuses highlighted in grey have been excluded from the model / *gli strati con le modalità dello stato vaccinale evidenziati in grigio sono stati esclusi dal modello*

prompting a need to study this group further, considering the good uptake in this group of scheduled vaccinations for the first two doses. There is currently limited evidence regarding the effectiveness of a booster[13,15] and in the literature there are limited short/medium-term assessments of its effectiveness in reducing hospitalization, intensive care admission, and mortality. Available data were built on the boosted Israeli population – comparable in size with the size of the population in our study – and indicate an important advantage with respect to symptomatic disease in the population over 60 years of age.[15] A study conducted on 270,000 people over 50 by the UK Health Security Agency led to the same conclusions.[24,25]
A recent study carried out on the Swedish population[17] shows that protection against infection wanes 4 months after vaccination, while protection against severe disease (e.g., hospitalization) lasts up until 9 months after vaccination, although a decrease in protection is already evident after 4 months. Similar results were also obtained in a study on the population of Lombardy.[18] These studies concluded underlining the importance of implementing a booster dose and they both preceded the appearance of the Omicron variant. Few articles so far have compared the severity of the Omicron variant compared to earlier ones; however, it seems to be more transmissible but less aggressive than the previous ones.[26] The present study, which refers to the period from 01.10.2021 to 31.12.2021, makes it possible to assess the importance of a booster dose, which began to be offered in Italy in October 2021, and of time elapsed since receipt of the main vaccination cycle right as the new variant was spreading in Lombardy and throughout Italy.
The findings of this study reveal a much more complex underlying information structure, characterized by various population segments where specific risk factors are concentrated.
In particular, table 2 shows that subjects who received two doses and have not yet received a booster identify a peculiar cluster of subjects: older subjects with a high chronic disease burden who, although they availed themselves of priority access to the initial course of vaccination, because of their characteristics, did not follow the same indication of priority in obtaining a booster dose.
At the beginning of the observation period, in the "2 doses received 7+ months earlier" category there were 73,392 subjects, of which 70,550 received a booster dose. At the end of the observation period, this category still included 74,152 subjects, because it was sustained by subjects that at the beginning of the period belonged to the "2 doses received 4+ months earlier" category (table 2). Evidence that receiving a booster is relevant to mitigate virus spread supports the fact that, because of its sociodemographic characteristics, this group is the

ideal target for specific public health interventions, including a study of the causes of the delay in obtaining a booster dose.

It must be pointed out that evidence of a specific hospitalization risk can be associated with another distinctive problem. Both with respect to the very high numbers and its characteristics, COVID-19-associated hospitalization cannot be currently compared to the first or second epidemic wave: whereas in the two previous waves, as in the third, longer epidemic phase, patients were mostly admitted due to problems involved with disease progression caused by pulmonary function being affected or onset of an inflammatory syndrome, two years after the beginning of the epidemic, the burden of conventional diseases, accompanied by the spread in the population of an extremely contagious variant, is channelling into COVID-19 hospital wards patients with acute situations linked with other diseases, who are at the same time infected by COVID-19. To date, hospital admissions *for* COVID-19 and hospitalizations *with* COVID-19 cannot be distinguished in the information systems used and developed for the epidemic up to this point.

Assuming, in any case, that there are segments of the population presenting specific chronic conditions who are less likely to access COVID-19 vaccination, the observed excess could partly be due to relapses requiring hospitalization in patients who are at the same time infected – with no symptoms or symptoms masked by the acute phase of another disease – by SARS-COV-2. The advantage in distinguishing these two pools of people remains to be understood, considering that, in any case, coexistence of COVID-19 in a subject with an acute condition is sure to change the course of the disease both clinically and by influencing the care setting and time to treat: acute abdomen in a subject with COVID-19 diagnosis at presentation surely does not play out like an acute abdomen without COVID-19.

Intensive care admissions for COVID-19, instead, are an index of a progression of SARS-COV-2 infection, since their definition is much more specific. In this select group of patients, although with the limitations due to the great number of observed cases, the protective effect of vaccination can be seen to be present even in a single dose and lasts more than seven months after receipt of the second dose.

On the other hand, comparison of the HR trend for all-cause deaths and Multiple Correspondence Analysis in the various groups corroborates the presence of an effect of other diseases. Furthermore, an increase in mortality can be noticed in subjects who were vaccinated more than 6 months earlier and, especially, more than 7 months earlier, which does not correspond to a similar increase in the risk of hospitalization for COVID-19.

The lack of booster uptake in a vaccinated group can be caused by a worsening of concurrent conditions– in subjects older than the rest of the vaccination groups – or due to initiation of concurrent treatment (for instance, chemotherapy or other treatments with drugs that target the immune system), which may have caused the failure to receive a booster and contributed to the increase in mortality.

A further thought is that the group that received two doses earliest is selected compared to those who received a booster, not only with respect to the burden of chronic conditions and age, but also as to deprivation: 16% of boosted subjects belong to the severely deprived category, as compared to 21% of subjects vaccinated more than 7 months earlier.

In short, the data presented here show that the group that was vaccinated over 7 months earlier concentrates various situations of disadvantage that include a mixture of sociodemographic conditions, clinical frailness, and isolation from the healthcare system, thus representing subjects at increased risk for various causes, including difficulty in accessing care due to saturation of hospital beds, which, particularly in the month of December, were mostly occupied by patients who had not taken up the vaccination campaign offer. This obviously identifies a potential problem of selection bias to which the excesses pointed out can be attributed, partly explainable by clinical conditions – 6% of subjects who received the vaccine more than 7 months earlier had heart failure, vs 1% of unvaccinated subjects and 3% of boosted subjects, 16% were diabetic vs 5% and 9%, respectively – partly by the effects of infection (which occurs more frequently, as observed in the literature), and partly by the failed access to treatment due to the situation in the hospitals.

We draw attention – using various data, including vaccination status – to a population group that accumulates a disadvantage not in order for it to be interpreted in terms of a causal link, but as a public health tool to orient multiple actions aimed at reducing health-related impacts. The characteristics of the group of subjects with delayed vaccination are exactly those describing the at-risk group which should have priority in the anti-COVID-19 campaign, which is substantially the same target as that of the seasonal flu vaccine and of emergency plans for the reduction of heat wave effects. As a matter of fact, due to all evidence of the selection phenomenon described above, 48% of the deaths observed in the cohort are concentrated in this group.

A picture of a substantial disparity of access of the unvaccinated population remains. The unvaccinated population does not appear to be solely made up of people who refuse the vaccine on cultural grounds, but also

and prevalently by a disadvantaged population, likely less educated to the need of assessing the complexity of the epidemic, and which healthcare institutions and media evidently have not been able to effectively relay information to.
It must also be underlined that the ten-point list produced by the Data Protection Authority slowed down actions of reinforcement/recruitment of non-uptakers – mediated by general practitioners – actions which are instead allowed to recapture non-uptakers in organized screenings, which as public healthcare measures are less effective, if only because they do not include the entire population, but only specific age groups.
The overall impact on the system is worsened by evidence that unvaccinated subjects have a 10 times greater risk of hospitalization for COVID-19 than those who received a booster, a 9-fold risk of entering intensive care for COVID-19, and a 3-fold risk of all-cause mortality.

STRENGTHS AND LIMITATIONS OF THE STUDY

Despite the descriptive nature of the study, studies of this type, which ATS Milan continuously implements and updates, count among their strong points the size of the included population, the well-established solidity of the information systems, and the methods employed to consolidate data.
An adaptation that is perhaps necessary is the need to produce rapid studies, adjusting the statistic-epidemiologic methodology to the available databases in order to provide findings supporting the decision to get vaccinated, and especially the undecided. These studies must then, in the long term, be formalized with more traditional designs to verify their results and consolidate them or revise them, identifying critical aspects in design that should not be replicated.
Rapid studies must serve to identify subcategories on which to focus attention. It is also necessary for these studies to be accompanied by the implementation of methods, since they do not start out with an ad-hoc design (controlled clinical trials), but from real-time evaluation of population data that have an underlying design constraint (in this case, a vaccine policy that calls for enrolment by age group) which must be carefully considered along with the short duration of the period, in order to reach interpretations that are not misleading.
But it must be once more pointed out that this study is based on individual data, which enable us to more accurately evaluate the effect of possible confounders and more easily interpret data in light of possible scenarios that need to be carefully pondered when the objective is to outline public health actions. We believe it is important to stress this point, because using aggregated data – although it presents fewer problems from the point of view of analysis – does not usually make it possible to assess problems in all their complexity.
In any case, the study still presents weak points derived from the complexity of the interactions between variables and the presence of confounders, because the regression models, in the absence of specific hypotheses to assess, cannot control them completely.
But the true limitation is system-related: even in the presence of strong evidence of a disadvantage, differently distributed on specific population groups, the current privacy law issued by the Data Protection Authority essentially prevents national healthcare organizations from taking effective action using vaccination status information together with other data (comorbidities, nationality, deprivation, age class) to produce lists of names that could be effectively managed by local healthcare services to retrieve segments of the population who fail to uptake vaccination due to lack of information.
In a setting where vaccination mandates struggle, internationally, to be applied – due to issues that vary depending on context – the identification of two population groups, i.e., unvaccinated/partially vaccinated subjects with a single dose and subjects vaccinated with two doses, that accumulate problems of disease burden is an important indication for public healthcare in order to limit the effects of the epidemic on people and hospitals. These are the two populations that engender the excess in hospitalizations and deaths, populations which should be contacted by local-based healthcare, which, with the advent of the NRRP and the establishment of community hospitals, will become the main actor in public healthcare management, making it possible to adopt timely targeted interventions.
In conclusion, studies that can be used to give voice to more effective strategies and targeted public health interventions are needed, not only because – if this epidemic should last – it will be necessary to develop a system integrating vaccine offer, treatments, and rapid surveillance systems in the population, in order to evaluate the effectiveness of developments on the field, but also with the aim of not finding ourselves constantly lagging behind and chasing the epidemic.

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