RASSEGNE E ARTICOLI

First SARS-CoV-2 vaccine booster and influenza vaccination: risk assessment of COVID-19 hospitalisation and death

Associazione tra prima dose booster anti-SARS-CoV-2 e vaccinazione antinfluenzale: valutazione del rischio di ricovero per COVID-19 e di decesso

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Abstract

Background: the influenza and SARS-CoV-2 viruses share a common respiratory symptomatology and transmission mode. COVID-19 and influenza R_0 overlapped in the first epidemic wave. In autumn 2021-winter 2022, the influenza epidemic had a delayed onset compared to pre-COVID-19 years and lower incidence rates than in the pre-pandemic period. The SARS-CoV-2 and influenza vaccination campaign overlapped in 2021-2022.
Objectives: to evaluate in the SARS-CoV-2 vaccinated cohort the effect of different timing of influenza vaccination on hospitalisations for COVID-19 and overall mortality.
Design: prospective cohort study.
Setting and participants: subjects aged 65 years or older who were administered the first booster dose of SARS-COV-2 vaccine between 01.10.2021 and 01.03.2022. Based on the date of influenza vaccination, subjects were divided into the following 4 different mutually exclusive groups: **1.** two vaccinations in the same vaccination session; **2.** influenza vaccination following SARS-CoV-2 vaccination; **3.** influenza vaccination preceding SARS-CoV-2 vaccination; **4.** no influenza vaccination. Using Cox regression models, hazard ratio (HR) and corresponding 95% confidence intervals (95% CI) of hospitalisation and death were estimated for the influenza-vaccinated subjects compared to influenza-unvaccinated subjects.
Main outcome measures: ordinary hospital admissions for COVID-19 and general mortality.
Results: the cohort included 618,964 subjects: 16.3% received two vaccinations in the same vaccination session, 8.5% received the influenza vaccination after SARS-CoV-2 vaccination, 33.9% received it before and 41.1% did not receive an influenza vaccination. Those vaccinated against both SARS-CoV-2 and influenza had a combined HR of 0.73 (0.62-0.86) of hospitalisation for COVID-19 and 0.55 (0.49-0.62) of overall mortality compared to those vaccinated against SARS-CoV-2 only.
Conclusions: influenza vaccination combined with SARS-CoV-2 vaccination increases the protective effect against hospitalisations and overall mortality compared to SARS-CoV-2 vaccination alone. Both organisational and communication actions aimed to promote and encourage vaccination are required.

Keywords: vaccine, anti-SARS-CoV-2, influenza vaccination, prevention

What is already known

- **During autumn 2021-winter 2022, circulation of SARS-COV-2 and influenza viruses was concomitant.**
- **Influenza vaccination achieved higher coverage than in previous years in the age group 65+ years.**
- **The administration of SARS-CoV-2 and influenza vaccinations was concomitant.**
- **Influenza vaccination is effective and safe in preventing hospitalisations and mortality due to influenza syndromes in the 65+ years old population.**

What this study adds

- **Using an analysis producing a design adjusted for immortal time bias, subjects who received both influenza and anti-SARS-CoV-2 vaccination have a reduced risk of hospitalisation for COVID-19 and death from all causes compared to subjects who did not receive the influenza vaccine.**
- **The advantage is relevant regardless of when the influenza vaccination was administered compared to anti-SARS-CoV-2 vaccine.**

Riassunto

Introduzione: i virus influenzale e SARS-CoV-2 hanno in comune la sintomatologia respiratoria e la modalità di trasmissione. Nell'autunno 2021-inverno 2022, l'epidemia influenzale ha avuto un inizio ritardato rispetto agli anni pre-COVID-19, con tassi d'incidenza inferiori rispetto al periodo pre-pandemico. Alla vaccinazione anti-SARS-CoV-2 si è sovrapposta la campagna vaccinale antinfluenzale 2021-2022.
Obiettivi: valutare nella coorte dei vaccinati con anti SARS-CoV-2 l'effetto delle diverse tempistiche di vaccinazione antinfluenzale sul rischio di ricovero ospedaliero per COVID-19 e sulla mortalità generale.
Disegno: studio di coorte prospettico.
Setting e partecipanti: soggetti di età superiore o uguale a 65 anni che afferiscono all'Agenzia per la tutela della salute della Città Metropolitana di Milano (ATS Milano), a cui è stata somministrata la prima dose booster di vaccino anti-SARS-CoV-2 nella finestra temporale dal 01.10.2021 al 01.03.2022. Sulla base della data della vaccinazione antinfluenzale, la coorte è stata suddivisa in 4 differenti gruppi mutuamente esclusivi: **1.** due vaccinazioni nella stessa seduta vaccinale; **2.** vaccinazione antinfluenzale successiva alla vaccinazione anti-SARS-CoV-2; **3.** vaccinazione antinfluenzale precedente alla vaccinazione anti-SARS-CoV-2; **4.** vaccinazione antinfluenza-

le non effettuata. Mediante modelli di regressione di Cox, sono stati stimati gli hazard ratio (HR) e i relativi intervalli di confidenza al 95% (IC95%) di ricovero e decesso per chi ha ricevuto la vaccinazione antinfluenzale rispetto a chi non l'ha ricevuta.
Principali misure di outcome: ricoveri ospedalieri ordinari per COVID-19 e mortalità generale.
Risultati: la coorte è composta da 618.964 soggetti che hanno ricevuto la prima dose booster del vaccino anti-SARS-CoV-2 tra il 01.10.2021 e il 01.03.2022. Il 16,3% ha ricevuto le due vaccinazioni nella stessa seduta vaccinale, l'8,5% ha ricevuto la vaccinazione antinfluenzale successivamente all'anti-SARS-COV-2, il 33,9% precedentemente, mentre il 41,1% non l'ha effettuata. I vaccinati con prima dose booster anti-SARS-CoV-2 e antinfluenzale presentano complessivamente un HR di 0,73 (0,62-0,86) di ricovero per COVID-19 e di 0,55 (0,49-0,62) di decesso per tutte le cause rispetto ai vaccinati solo con anti-SARS-CoV-2.
Conclusioni: la vaccinazione antinfluenzale associata alla vaccinazione anti-SARS-CoV-2 è legata a un aumento dell'effetto protettivo rispetto agli esiti rappresentati dai ricoveri per COVID-19 e dal decesso per tutte le cause rispetto alla sola vaccinazione anti-SARS-CoV-2. È indispensabile un ingaggio attivo della popolazione da parte del Servizio sanitario con azioni sia organizzative sia di comunicazione tese a valorizzare i benefici per la salute delle politiche vaccinali offerte in sanità pubblica.

Parole chiave: vaccinazione, anti-SARS-CoV-2, antinfluenzale, prevenzione

Background

The influenza and SARS-CoV-2 viruses share a common respiratory symptomatology and mode of transmission, with an R_0[1] which in the first epidemic wave of COVID-19 completely overlapped with that of influenza, but later distinguished itself as being more contagious. In the pre-SARS-CoV-2 pandemic era, recommendations for the prevention and control of influenza - seasonal vaccination, hand washing, use of face masks, self-isolation in the presence of suspected symptoms - were largely disregarded, with immunisation levels in the over-65 population well below the recommended level of 75%. Although they have many similar characteristics, the two viruses have a very different pathogenicity. In the past, in Italy, about 5-6 million infections each year and almost 20,000 deaths each season were attributed to influenza:[2] the SARS-CoV-2 epidemic, after almost 3 years of waves characterised by variants with different pathogenicity, caused almost 22 million ascertained cases and more than 175,000 deaths in total over 3 years.
The SARS-CoV-2 epidemic profoundly changed the course of the influenza epidemic. The first interaction between the two epidemics took place in 2020-2021 and, although there was much concern in the autumn of 2020 about the simultaneous circulation of the influenza virus and the delta variant of SARS-CoV-2, the actual worldwide incidence of influenza viruses was very low. Surveillance data from the InfluNet system,[3] but also from the ECDC,[4] showed that there was essentially no seasonal influenza epidemic in 2020-2021. At the same time, due to a number of critical issues in the availability of influenza vaccines, the vaccination campaign started very late, even though it reached a higher level of coverage in the over-65-year age group than in the previous season. The reduced circulation of influenza viruses in the 2020-2021 season, however, is not attributable to an increase in vaccination coverage, which was in any case achieved late, but to the combination of lockdown measures, closure of businesses and schools, restriction of international travel, and the presence of personal protective measures represented by the mandatory use of face masks and social distancing, combined with the recommendation to wash hands frequently.
In autumn 2021-winter 2022, the influenza epidemic had a delayed onset compared to the pre-COVID-19 years and incidence rates were higher than in 2020-2021, but certainly much lower than in the 2019-2020 influenza epidemic, affecting about 6 million Italians.[3]
An important aspect to assess is that the SARS-CoV-2 vaccination, now in its third dose, overlapped with the 2021-2022 influenza vaccination campaign, as the Italian Ministry of Health recommended co-administration with the SARS-CoV-2 vaccine for at-risk individuals.
Recent works have suggested that influenza vaccination may confer some protection against adverse outcomes of SARS-CoV-2 infection.[5-8] In support, several biological mechanisms have been hypothesised, such as induction of innate immunity[9] and trained immunity,[10] vaccine-associated viral interference,[11] utilisation of immunological memory as a response to novel pathogens (original antigenic sin),[12] activation of a non-specific response[13,14] or recognition of SARS-CoV-2 as influenza-like.[15] On the other hand, the administration of both vaccinations in the same vaccination session is logistically and organisationally more efficient,[16] besides being safe. Against this background, it is interesting to assess whether the administration of the influenza vaccination can confer additional protection compared to SARS-CoV-2 vaccination alone.

Objectives

The aim of this work is to evaluate, in the cohort of vaccinees aged 65 years and older with the first booster dose of SARS-CoV-2 vaccine, the effect of influenza vaccination (administered before, after or at the same time as the first booster dose) on hospitalisation for COVID-19 and overall mortality. The study was conducted in the time window from 01.10.2021 (starting date of administration of the first anti-SARS-CoV-2 booster dose) to 01.03.2022 (starting date of administration of the second anti-SARS-CoV-2 booster dose).

Materials and Methods

The population included in the study has been described in two previous studies[17,18] and is the population assisted by the Agency for Health Protection of the Metropolitan Area of Milan (ATS of Milan) residing in the provinces of Milan and Lodi (Lombardy Region, Northern Italy) aged 65 years or older and alive on 01.10.2021.

All nursing home residents were excluded from the population, as the vaccination campaign is organised differently for them than for the rest of the population served by the ATS of Milan. In addition, in order to design a study that had no problems with the definition of COVID-19 vaccination allocation and to avoid possible confounding effects due to hybrid immunity,[19] all subjects who had been COVID-19 cases before receiving the first booster dose were excluded. The subjects were then followed from inclusion in the study (assisted by and residing in ATS of Milan alive on 01.10.2021) until the end of observation (01.03.2022).

The information derived from the New Regional Registry Office (NAR) of assisted persons was integrated with information from the permanent georeferencing system, developed and maintained by the Epidemiology Unit of ATS of Milano, which allows the inclusion of information derived from the 2011 Italian Census, in particular, the deprivation index calculated on the basis of the census tract. The presence of comorbidities was derived using the assisted database (BDA) of the chronic patient[20,21] created according to the Lombardy Region guidelines and algorithm.

The database from the previous study was supplemented with the vaccine flow and only subjects who underwent the first booster dose in the time window of the study (01.10.2021-01.03.2022) were selected.

COVID-19 cases and their date of diagnosis were identified between 01.10.2021 and 01.03.2022 by means of data from the information system of swab-positive subjects of the Lombardy Region. This made it possible to position the vaccination history with respect to the disease of each patient included in the cohort. In this way, the cohort was divided into four mutually exclusive groups:

1. two vaccinations in the same vaccination session (booster and influenza);
2. influenza vaccination following SARS-CoV-2 vaccination;
3. influenza vaccination prior to SARS-CoV-2 vaccination;
4. no influenza vaccination.

Hospital admissions for COVID-19 during the five-month follow-up period were identified by integrating the hospital admissions flow (SDO) updated to May 2022, using COVID-19-specific codings, with the dedicated flow from the hospitals that detects all new admissions for COVID-19 on a daily basis, updated daily with new admissions. In order to limit the analyses to only adverse outcomes due to SARS-CoV-2 infection, ordinary admissions of patients for whom COVID-19 was not the primary cause of hospitalisation were excluded.

The living status was updated periodically - with a delay of about one week - thanks to the integration of the municipal registers with the registry of patients.

Using the overall integration of all sources described, by deterministic record linkage via an anonymised unique code, each patient was associated with the living status and hospitalisation for COVID-19 (updated 01.03.2022) occurring after vaccination with the first booster dose during follow-up. The censoring date was either the end of follow-up or death if occurring earlier. For analyses concerning hospitalisation only, if the hospitalisation occurred before the influenza vaccination, the observation time was censored at the date of hospitalisation.

Time to hospitalisation and death were analysed using Cox regression models, which assesses exposure by adjusting for gender, age (included in five-year classes and with the reference category consisting of all subjects aged 65-69 years), socioeconomic status, citizenship and number of comorbidities detected by the Lombardy Region BDA.[20,21]

Considering that the cohort was recruited on 01.10.2021, the day on which the SARS-CoV-2 booster vaccination started, and influenza vaccination started on 04.10.2021, a delayed entry approach was used at the date of the anti-SARS-CoV-2 vaccination (so as to avoid what is known as immortal time bias)[22] and the time dependence of the influenza vaccination with respect to the COVID vaccination was taken into account. Effect estimates are expressed in terms of hazard ratios (HR) and corresponding 95% confidence intervals (CI95%).

Results

The cohort consisted of 618,964 subjects who received the first booster dose of the SARS-CoV-2 vaccine between 01.10.2021 and 01.03.2022 and who had

not previously been COVID-19 cases: as of 01.01.2022, 97% of the subjects in the cohort had received the first booster dose.

Based on the date of flu vaccination, the cohort was composed as follows:

1. 101,230 (16.3%) subjects with two vaccinations in the same vaccination session;

2. 52,924 (8.5%) subjects with influenza vaccination following SARS-CoV-2 vaccination;

3. 209,935 (33.9%) subjects with influenza vaccination preceding SARS-CoV-2 vaccination;

4. 254,875 (41.1%) subjects who did not have influenza vaccination.

The coverage in the 2021-2022 influenza vaccination campaign of individuals aged 65 years or older in this population participating in the first anti-SARS-CoV-2 booster dose was therefore 59%.

Table 1 shows the distribution of the sociodemographic characteristics of the 4 population groups. The group of the unvaccinated and those who got the flu vaccination earlier has a higher prevalence of women, is younger (5 years on average), and has fewer comorbidities than those who got the vaccination synchronously or later. The group that did not receive the flu vaccination has a higher prevalence of foreigners.

Table 2 shows the distribution of the main chronic conditions, confirming that all individual chronic conditions are less represented in the group of those not vaccinated with the influenza vaccine. At the same time, subjects with comorbidities have a higher percentage of both synchronous and asynchronous vaccinations than subjects with comorbidities without vaccination.

In the study cohort, the risk of hospitalisation for COVID-19 and all-cause mortality were assessed.

The HR calculated by means of the multivariate Cox model, corrected for immortal time bias (table 3), yields an estimate for admissions for COVID-19 of 0.73 (0.62-0.86) - the biased estimate of the HR is 0.71 (0.67-075). For deaths from all causes, the estimate for those vaccinated only against SARS-CoV-2 is 0.55 (0.49-0.62), compared to the biased estimate of 0.65 (0.61-0.70).

The comparison, using the division of the cohort into four groups and the non-influenza vaccinated as the reference category, shows similar trends of risk reduction, uniform in the vaccinated group, regardless of when the influenza vaccination took place compared to the first booster dose.

Analysis stratified by presence or absence of comorbidities shows that chronic conditions do not represent an effect modifier, as estimates are essentially very similar, all other confounders being equal. However, non-significant estimates with respect to protection for COVID-19 admissions are observed in the group without comorbidities.

Discussion

This study highlights that influenza vaccination combined with SARS-CoV-2 vaccination increases the protective effect with respect to the outcomes of hospitalisations for COVID-19 and death from all causes. The benefit for the groups with influenza vaccination, regardless of the timing of influenza vaccination versus SARS-CoV-2 vaccination, is significant and shows a reduction in hospitalisations for COVID-19 (HR 0.73; 95%CI 0.62-0.86) and mortality (HR 0.55; 95%CI 0.49-0.62) of approximately 30%-40% and adds further information to the complex scenario of vaccine policy development in public health.

In the literature, there are several papers highlighting a decrease in hospitalisations and mortality in the influenza-vaccinated population.[5-8] In a recent paper, Hosseini-Moghaddam et al.[23] note a decrease in mortality and hospitalisations due to COVID-19 in the influenza-vaccinated population, highlighting how this may be related to healthy vaccinee bias. However, there are no evaluations of the joint effects of vaccination at the population level. The only study dealing with this topic, conducted on a few dozen healthcare workers, showed an increase in the SARS-CoV-2-specific T-lymphocyte-mediated immune memory response in subjects vaccinated for seasonal influenza.[24] Another study including 64 subjects given the combined BNT162b2 and influenza vaccine did not reveal any differences in adverse events or anti-Spike antibody levels.[25]

The influenza and SARS-COV-2 viruses are similar in terms of symptomatology and pathogenicity (especially with regard to the new SARS-CoV-2 viral variants), but are currently different in terms of contagiousness, as the new SARS-CoV-2 variants are more contagious than the influenza virus; also in view of the fact that the spread of the two viruses occurs in the same time window, vaccination campaigns must necessarily coexist and complement each other.

Based on information derived from a single hospital, Pascucci et al. (2022)[26] attempted to outline scenarios of influenza vaccination coverage and trends in the COVID-19 era in healthcare workers and highlighted significant decreases in coverage in the 2021-2022 influenza epidemic season compared to the 2020-2021 season, as well as the absence of changes in influenza coverage before and after the COVID-19 pandemic. They concluded that, once the acute phase of the emergency – to which the increase in influenza vaccination in the 2020-2021 season can be attributed – was over, healthcare workers appeared to be reluctant to vaccinate against influenza. This phenomenon

Characteristics	Synchronous influenza vaccine		Influenza vaccine following SARS-CoV-2 vaccine		Influenza vaccine preceding SARS-CoV-2 vaccine		No influenza vaccine		Total	
	N.	%	N.	%	N.	%	N.	%	N.	%
Gender										
Males	46,367	45.8	23,436	44.3	90,858	43.3	107,127	42.0	267,788	43.3
Females	54,863	54.2	29,488	55.7	119,077	56.7	147,748	58.0	351,176	56.7
Age group										
Average - median (SD)	80.4-82.0 (7.4)		79.6-81.0 (7.5)		75.2-74.0 (6.5)		75.5-74.0 (7.4)		76.5-76.0 (7.5)	
[65,70)	11,699	11.6	6,755	12.8	44,001	21.0	68,403	26.8	130,858	21.1
[70,75)	11,909	11.8	8,031	15.2	61,074	29.1	61,278	24.0	142,292	23.0
[75,80)	11,772	11.6	7,086	13.4	58,486	27.9	49,348	19.4	126,692	20.5
[85,90)	35,673	35.2	16,978	32.1	26,261	12.5	41,247	16.2	120,159	19.4
[90,95)	20,608	20.4	9,640	18.2	13,112	6.2	22,854	9.0	66,214	10.7
95+	9,569	9.5	4,434	8.4	7,001	3.3	11,745	4.6	32,749	5.3
Local Health Authority										
Milano	51,483	50.9	21,108	39.9	67,243	32.0	100,251	39.3	240,085	38.8
Rhodense	14,449	14.3	7,003	13.2	32,289	15.4	35,763	14.0	89,504	14.5
Ovest Milano	7,256	7.2	7,418	14.0	34,555	16.5	35,671	14.0	84,900	13.7
Nord Milano	5,950	5.9	4,915	9.3	19,276	9.2	21,976	8.6	52,117	8.4
Melegnano	15,334	15.1	9,707	18.3	41,836	19.9	44,090	17.3	110,967	17.9
Lodi	6,758	6.7	2,773	5.2	14,736	7.0	17,124	6.7	41,391	6.7
Deprivation Index										
Very affluent	26,072	25.8	12,779	24.1	45,452	21.7	55,070	21.6	139,373	22.5
Affluent	19,386	19.2	10,743	20.3	43,040	20.5	49,778	19.5	122,947	19.9
Average	17,916	17.7	10,325	19.5	42,558	20.3	49,128	19.3	119,927	19.4
Deprived	17,570	17.4	9,583	18.1	39,211	18.7	47,079	18.5	113,443	18.3
Very deprived	18,179	18.0	8,486	16.0	35,251	16.8	46,901	18.4	108,817	17.6
Missing	2,107	2.1	1,008	1.9	4,423	2.1	6,919	2.7	14,457	2.3
Citizenship										
Italian	99,699	98.5	52,499	99.2	207,494	98.8	246,883	96.9	606,575	98.0
Foreigner	1,531	1.5	425	0.8	2,441	1.2	7,992	3.1	12,389	2.0
Comorbidity										
None	16,132	15.9	8,035	15.2	41,413	19.7	74,113	29.1	139,693	22.6
1	23,330	23.0	12,268	23.2	54,895	26.1	67,944	26.7	158,437	25.6
2	21,109	20.9	11,364	21.5	44,378	21.1	47,589	18.7	124,440	20.1
3	16,615	16.4	8,770	16.6	30,793	14.7	30,094	11.8	86,272	13.9
4+	24,044	23.8	12,487	23.6	38,456	18.3	35,135	13.8	110,122	17.8
Total	**101,230**		**52,924**		**209,935**		**254,875**		**618,964**	

Table 1. Characteristics of the ATS Milan population over 65 years of age with a third SARS-CoV-2 vaccine dose according to influenza vaccination status/timing.
Tabella 1. Caratteristiche della popolazione della ATS di Milano di età uguale o superiore a 65 anni con terza dose vaccinale anti-SARS-CoV-2.

Characteristics	Synchronous influenza vaccine		Influenza vaccine following SARS-CoV-2 vaccine		Influenza vaccine preciding SARS-CoV-2 vaccine		No influenza vaccine		Total	
	N.	%	N.	%	N.	%	N.	%	N.	%
Transplanted										
Absent	100,954	99.7	52,634	99.5	209,562	99.8	254,347	99.8	617,497	99.8
Present	276	0.3	290	0.5	373	0.2	528	0.2	1,467	0.2
Immunocompromised										
Absent	99,524	98.3	51,775	97.8	207,621	98.9	251,745	98.8	610,665	98.7
Present	1,706	1.7	1,149	2.2	2,314	1.1	3,130	1.2	8,299	1.3
Autoimmune diseases										
Absent	99,836	98.6	51,969	98.2	207,254	98.7	251,806	98.8	610,865	98.7
Present	1,394	1.4	955	1.8	2,681	1.3	3,069	1.2	8,099	1.3
Diabetes										
Absent	82,812	81.8	43,919	83.0	176,930	84.3	221,207	86.8	524,868	84.8
Present	18,418	18.2	9,005	17.0	33,005	15.7	33,668	13.2	94,096	15.2
Hypertension										
Absent	34,645	34.2	17,748	33.5	81,890	39.0	123,417	48.4	257,700	41.6
Present	66,585	65.8	35,176	66.5	128,045	61.0	13,1458	51.6	361,264	58.4
Chronic kidney infection/Dialysis										
Absent	98,049	96.9	51,143	96.6	205,380	97.8	250,032	98.1	604,604	97.7
Present	3,181	3.1	1,781	3.4	4,555	2.2	4,843	1.9	14,360	2.3
COPD										
Absent	93,280	92.1	48,788	92.2	194,525	92.7	242,592	95.2	579,185	93.6
Present	7,950	7.9	4,136	7.8	15,410	7.3	12,283	4.8	39,779	6.4
Neurological diseases										
Absent	98,101	96.9	51,580	97.5	205,848	98.1	249,749	98.0	605,278	97.8
Present	3,129	3.1	1,344	2.5	4,087	1.9	5,126	2.0	13,686	2.2
Cirrhosis										
Absent	100,477	99.3	52,565	99.3	208,707	99.4	253,438	99.4	615,187	99.4
Present	753	0.7	359	0.7	1,228	0.6	1,437	0.6	3,777	0.6
Chronic inflammatory bowel diseases										
Absent	100,296	99.1	52,405	99.0	207,919	99.0	253,034	99.3	613,654	99.1
Present	934	0.9	519	1.0	2,016	1.0	1841	0.7	5,310	0.9
Heart diseases										
Absent	69,304	68.5	36,333	68.7	156,887	74.7	202,831	79.6	465,355	75.2
Present	31,926	31.5	16,591	31.3	53,048	25.3	52,044	20.4	153,609	24.8
Arterial vascular disease										
Absent	98,208	97.0	51,416	97.2	205,017	97.7	249,857	98.0	604,498	97.7
Present	3,022	3.0	1,508	2.8	4,918	2.3	5,018	2.0	14,466	2.3
Heart failure										
Absent	94,283	93.1	49,557	93.6	200,301	95.4	245,063	96.2	589,204	95.2
Present	6,947	6.9	3,367	6.4	9,634	4.6	9,812	3.8	29,760	4.8
Cerebrovascular disease										
Absent	95,804	94.6	50,335	95.1	201,804	96.1	245,599	96.4	593,542	95.9
Present	5,426	5.4	2,589	4.9	8,131	3.9	9,276	3.6	25,422	4.1
Total	**101,230**		**52,924**		**209,935**		**254,875**		**618,964**	

Table 2. Distribution of main comorbidities in the ATS Milan population over 65 years of age with a third SARS-CoV-2 vaccine dose according to influenza vaccination status/timing.
Tabella 2. Distribuzione delle principali comorbidità della popolazione della ATS di Milano di età uguale o superiore a 65 anni con terza dose vaccinale anti-SARS-CoV-2.

Vaccine status	Hospitalisation for COVID-19		Deaths for all causes	
	Events/days (10^3)	HR (95%CI)	Events/days (10^3)	HR (95%CI)
Influenza vaccination				
Not carried out	1,795/18,242.3	1#	1,294/18,263.8	1#
Synchronous	1,315/10,793.0	0.74 (0.62-0.89)	930/10,811.3	0.56 (0.49-0.63)
Following	570/5,677.0	0.55 (0.42-0.72)	396/5,685.0	0.40 (0.33-0.48)
Preceding	1,065/14,993.3	0.64 (0.53-0.76)	672/15,009.4	0.47 (0.41-0.54)
No comorbidities**				
Influenza vaccination				
Not carried out	181/4,986.9	1#	132/4,989.0	1#
Synchronous	93/1,647.6	0.92 (0.62-1.38)	60/1649.1	0.39 (0.24-0.65)
Following	34/824.1	0.91 (0.50-1.65)	19/824.7	0.18 (0.08-0.41)
Preceding	70/2,871.4	0.75 (0.50-1.12)	36/2,872.6	0.29 (0.17-0.50)
At least one comorbidity**				
Influenza vaccination				
Not carried out	1,614/13,255.5	1#	1,162/13,274.8	1#
Synchronous	1,222/9,145.4	0.74 (0.61-0.89)	870/9,162.2	0.60 (0.52-0.68)
Following	536/4,853.0	0.55 (0.41-0.72)	377/4,860.3	0.44 (0.36-0.53)
Preceding	995/12,121.9	0.64 (0.53-0.77)	636/12,136.8	0.51 (0.44-0.59)
Influenza vaccination				
No	1,795/18,242.3	1#	1,294/18,263.8	1#
Yes	2,950/31,463.8	0.73 (0.62-0.86)	1,998/31,505.7	0.55 (0.49-0.62)

* Cox models adjusted for gender, age (five-year classes), socioeconomic status, and citizenship (Italian vs foreign), number of comorbidities. Cox models included delayed entry at the date of SARS-CoV-2 vaccination and influenza vaccination as a time-dependent variable in the model / *modelli di Cox aggiustati per genere, età (classi quinquennali), stato socioeconomico e cittadinanza (italiana vs straniera), numero di comorbidità e che includono nel modello il delayed entry alla data della vaccinazione anti-SARS-CoV-2 e la vaccinazione antinfluenzale come variabile dipendente dal tempo*

** the number of comorbidities is not included in the model / *nel modello non è incluso il termine numero di comorbidità*

reference category / *categoria di riferimento*

Table 3. Hazard ratio* (HR) and corresponding 95% confidence intervals (CI95%) of hospitalisation for COVID-19 and death from all causes by vaccine status at 01.03.2022 in the population over 65 years of age receiving a third SARS-CoV-2 vaccine dose.

Tabella 3. Hazard ratio* (HR) e corrispondenti intervalli di confidenza al 95% (IC95%) di ricovero per COVID-19 e decesso per tutte le cause per stato vaccinale al 01.03.2022 nella popolazione al di sopra dei 65 anni sottoposta a terza dose vaccinale anti-SARS-CoV-2.

may be attributable to the lack of a strong preventive culture among healthcare workers.

Notwithstanding the indisputable lack of a preventive vaccine culture, which is in part due to the system's poor communication capacity of and the confusion linked to different visions on the efficacy of vaccines, what is certainly becoming apparent, albeit in the face of various problems of interpretation, is that the population that gets vaccinated has sociodemographic and behavioural characteristics and specific chronic conditions burdens that condition its distribution into groups with different evolutions in terms of the outcomes detected.[17,18,27] At present, we are only able to capture the effects of these differences retrospectively, although the timing of these assessments, thanks to the availability of information in health information systems, is becoming much shorter, making it almost possible to use them contextually to modulate information and active recruitment campaigns. The limits to this new possibility are mainly represented by publication times - as any evidence must undergo a peer review process and using data without an accredited review is morally objectionable - and by privacy regulations that often prevent public health from reaching the excluded targets on which early action would be most effective, often in terms of reducing mortality.

This type of study may present biases related to possible selection bias in the population. In this context, an attempt was made to select the cohort in order to minimise the magnitude of said bias. In fact, the study population consists of subjects who are largely

attentive to the vaccination strategy to reduce the effects of COVID-19, who have already undergone 3 different vaccinations, in a very controversial information and also political climate in which communication with respect to vaccination was contradictory. The comparison is made within a cohort of subjects who, out of conviction or compulsion, got vaccinated themselves and did so in the face of an element of strong pressure (hundreds of thousands of hospitalisations and deaths). That the influenza epidemic, on the other hand, is considered not as strong an element of pressure is represented by the fact that in this selected and engaged cohort, but still a population cohort, vaccination coverage reached 59% - compared to a 65+ coverage of 55% in 2019-2022[28] -, despite influenza vaccination being among the essential levels of care defined by the Italian Ministry of Health and having a target of 75%. The fact that we took into account only admissions for COVID-19, moreover, minimised the bias due to a different ability in the two groups to detect cases of COVID-19 admissions in individuals admitted for other reasons. Furthermore, it should be noted that the exclusion by design of subjects admitted to nursing homes and those who had already contracted COVID-19 may constitute a limitation to the generalisability of the study. It should also be emphasised that the different vaccination settings are made up of different populations in terms of socioeconomic characteristics, frailty, and age: these factors are also associated with the outcomes under study and not taking them into account in the analysis may produce biased estimates.

A very important piece of information, on the other hand, is that the effect of reducing hospitalisations and mortality can be attributed to the addition of influenza vaccination to SARS-CoV-2 vaccination, which has evidence of advantage in very selected cohorts (patients with severe heart disease, cancer patients undergoing treatment) in the literature.[29-31] Whether the effect is related to the activation of T-lymphocyte populations that intervene in the progression of SARS-CoV-2 infection by reducing the effects of COVID-19 or whether it is related to reducing the effects of influenza virus infection is not an answer this study can give.

Conclusions

The opportunity to develop coherent vaccination strategies to increase the population-wide advantage over serious outcomes is the most relevant conclusion of this work. Losing further portions of the elderly population, already hard hit by the SARS-CoV-2 epidemic, due to the difficulties the prevention system has in increasing uptake of vaccination programmes of known advantage, such as the influenza vaccine programme, is a major concern calling for careful consideration.

The results of this work suggest that, with the availability of effective and safe vaccines, well-structured building of immunity at the population level is key to achieve health gains. To this end, an active engagement of the population by the healthcare service is indispensable, including both organisational and communication actions aimed at enhancing the now indisputable health benefits of vaccination policies offered by public healthcare.

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