Short-term mortality following COVID-19 vaccination in Bologna, Italy: a one-year study

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ABSTRACT

The main objective of the study is to assess whether there is an increased risk of mortality in the days following the administration of COVID-19 vaccines in Bologna Health Authority in the first year of COVID-19 vaccination campaign. A secondary objective was to describe causes of deaths occurred in the days after vaccination. We conducted a retrospective observational study on all residents of Bologna Health Authority who received at least one COVID-19 vaccination dose from December 27, 2020 to December 31, 2021 and compared mortality in the 3, 7, 14 30 days after vaccination (risk interval) with the mortality in the period of the same length (3, 7, 14 and 30 days) beyond the 30th day after the last dose of vaccination (control interval). The cohort included 717,538 people. The mortality rate was 2.24 per 100 person-years during the 30 days risk interval vs 2.72 in the control interval with an adjusted incidence rate ratio equal to 0.76 (95% CI: 0.70–0.83, p < 0.001). The risk of mortality is significantly lower (p < 0.001) also in the 3, 7, 14 days risk intervals than in the control intervals. This study shows that there is no increase in mortality in the short-term period after COVID-19 vaccines.

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1. Introduction

Since the emergence of COVID-19, the world has taken significant measures to cope with this disease. Global efforts have been made to develop different vaccines to curb the pandemic [1] and after less than a year from the start of the pandemic, multiple vaccines were developed. Between the end of 2020 and the beginning of 2021, several of them received emergency use approval by the Food and Drug Administration and conditional marketing authorization by the European Medicines Agency. Both mRNA (BNT162b2, Pfizer-BioNtech and mRNA-1273, Moderna) and AdenoVirus vaccines (ChAdOx1-S, Oxford/Astrazeneca and Ad26

CoV2-S, Johnson & Johnson) proved to be highly effective and safe in large randomized phase 3 clinical trials [2–5].

However, rare outcomes associated with vaccines may not appear from the phase 3 trials because of the lack of sufficient power, because of the short follow up time of the studies and because the population included may differ from the population receiving the vaccine. For the same reasons, fatal events associated to vaccination may remain undisclosed in the premarket trial.

At the same time, with the large vaccination campaign there are inevitably some cases whose death is close in time to their COVID-19 vaccine, raising questions on a possible relation between death and recent vaccination. These concurrent events receive great resonance in the media, generating suspicion and concerns in the population [6,7] that likely attribute a causal link between the two events.

Thus, monitoring vaccine safety is of utmost importance to protect the intended population and to reduce fears which might otherwise reduce vaccination adherence [8] and contribute to vaccine hesitancy [6,7].

Various surveillance systems in different countries have been monitoring vaccination safety since the beginning of the vaccination campaign and by now have received numerous reports of fatal

events occurring after vaccination although they mostly did not result to be correlated to vaccination [9–12] in post-mortem investigation. Causal relationship was established only in very rare cases, such as for deaths linked to thrombotic events [13,14]. However, besides surveillance systems and a few post-mortem investigation reports [13], evidence on the risk of mortality after vaccination is scanty. Until now, few studies have been conducted to assess whether mortality is increased following COVID-19 vaccination [15–17].

We conducted a study with the main objective of assessing whether there is an increased risk of mortality in the days following the administration of COVID-19 vaccines in the population of Bologna Health Authority from December 27, 2020 to December 31, 2021. A secondary objective was to describe the characteristics of deaths and causes of death occurred after vaccination.

2. Methods

2.1. Study design setting and population

We conducted a retrospective cohort study in the vaccinated population of Bologna Health Authority (BHA). BHA is the local health care organization in charge of prevention and care of the population (about 890,000 inhabitants) living in a territory situated in Northern Italy which comprises Bologna Municipality, the main town, and other 44 municipalities. In BHA, as elsewhere in Italy, COVID-19 vaccination campaign started on December 27, 2020 and addressed first health care workers, the elderly and the frailest subjects and later was gradually extended in a schedule based primarily on age. Since December 2021 also 5–11 years old children were included as potential beneficiary of the vaccination. BNT162b2 was the first vaccine to be authorized, but shortly afterward also mRNA-1273 and ChAdOx1-S were available. Ad26 CoV2-S was authorized mid-March. Apart from some age criteria associated with the use of ChAdOx1-S, the choice of which vaccine to administer depended mainly on the product availability and for this reason BNT162b2 was the most frequently distributed. Nevertheless, due to lighter conservation requirements mRNA-1273 was preferred by general practitioners, for home administration and by nursing homes, whereas the Public Health Department that was in charge of the distribution of vaccines to the general population used mainly BNT162b2.

We included all residents who received at least one dose of any COVID-19 vaccine authorized in Italy from December 27, 2020 to December 31, 2021. We excluded residents that moved to municipalities of other health authorities because of the uncertainty regarding their life status. The study population was identified by using the BHA COVID-19 Vaccination registry. This is a locally based register that contains information about type of vaccine, number of doses, dates and venue of administration for all subjects that received a dose of vaccine in the BHA area.

2.2. Exposure period

Participants were followed from the date of their last vaccination (day 1) for 60 days or to the date of death or to December 31, 2021 whichever occurred first. The follow-up period of each participant was divided in risk intervals and non-risk intervals (i.e. control intervals). We considered as risk interval the period within 3, 7, 14 and 30 days from day 1 and as control interval the period of the same length (3, 7, 14 and 30 days) of follow-up beyond the 30th day after the last dose of vaccination. We considered the last dose of the vaccine, assuming that the short-term mortality did not depend on the number of doses.

2.3. Outcomes and additional variables

The main outcome of the study was death from all causes. Deaths were identified by using Bologna's Causes of Death Registry which covers all the deaths of the residents of the BHA catchment area and provides information about socio-demographic characteristics and on date, place, circumstances and initial cause of death. The cause of death derives from information recorded in the medical section of the death certificate and is classified according to the tenth revision of the ICD (International Classification of Diseases) and coded according to the WHO rules. All information is collected following national protocols. At the time of the study, the collection of all deaths that occurred during the study year, was considered complete.

We also collected additional variables to characterise the study population and/or to consider as confounders. In particular, we retrieved comorbidities of the previous two years (cardiovascular, cerebrovascular, respiratory system diseases, tumors, diabetes, hypertension, Parkinson, dementia, mental health disorders, renal failure) of the population from the local frailty database which, in turn derives from hospital discharge records, exemption and pharmaceutical archives of 2019 and 2020. This database was also used to retrieve the frailty index. The index is obtained from a multiple predictive model and is attributed to each adult resident in BHA predicting the probability of urgent hospitalization or death in the following year [18]. It ranges from 0 to 100 and is categorized into 5 classes of frailty: very low (0–5.99), low (6–29.99), medium (30–49.99), high (50–79.99), and very high (80–100). The frailty index database is available only for 18+ residents.

Information about SARS-CoV-2 infection was retrieved from a local surveillance database which contains demographic, clinical and epidemiological characteristics of all confirmed cases of SARS-CoV-2 infection in the BHA area. At the time of the study, confirmation of SARS-CoV-2 cases required a RT-PCR test using an oral and/or nasopharyngeal swab. All archives were linked with the BHA COVID-19 Vaccination registry by using the fiscal code, a unique identification code that is provided to all Italian citizens.

2.4. Ethics statement

This is a retrospective observational study where no new diagnostic tool or drug treatment was provided to any participant to conduct this study. Participant data were collected as part of standard public health surveillance activities. In accordance to Italian laws about personal data, informed consent was not required because unfeasible given the large sample size. Data were anonymized prior to the analyses after database linkage was done. Only one author conducting database linkage had access to patients identifying information.

2.5. Statistical analysis

We computed frequencies of baseline characteristics of the study population and cases. For each risk interval we calculated the rate of mortality and compared with the corresponding control interval rate. We estimated raw and adjusted IRRs (incidence rate ratio) with 95% confidence interval (CI). Adjusted estimates were obtained by applying a multivariable Poisson regression model. The model included: age class (<18, 18–40, 41–64, 65–74, 75–80, 81–84, 85–90, >90 years), day of week and period of vaccination. The study period was divided in three periods (27 December 2020–30 April 2021; 1 May- 31 August 2021 and 1 September- 31 December 2021) to take account of differences in mortality across the year; each subject was attributed a period according to the date of the last dose. In a secondary step we conducted a stratified analysis where a multivariable Poisson regression model

was run also by gender, age class, type of vaccine, and excluding patients with a SARS-CoV-2 infection. The model included the same covariates as the main model, except for age which was continuous in the stratified analyses by age class. We replicated the analyses also after excluding all subjects that had a diagnosis of SARS-CoV-2 infection during the follow-up period because a protective effect of vaccination for COVID-19-related deaths was expected beyond the first week from the administration. In addition, the analyses were repeated in the adult (>18 years old) population using a model with frailty index, day of week and period of vaccination as covariates.

All analyses were performed using STATA 16.1, Texas USA software.

3. Results

Between December 27, 2020 and December 31, 2021, 717,538 subjects resident in BHA received at least one dose of one of the authorized vaccines against COVID-19. Table 1 shows the main demographic characteristics of the study populations and the type of vaccine that was administered as last dose.

During the follow-up period there have been 1152 deaths in the 30 days risk interval and 1015 in the 30 days control interval. Table 2 shows the main demographic and clinical characteristics and type of vaccine of the deaths. Deaths of risk and control intervals were mostly females and aged 85 or over. The most frequent comorbidities were tumours followed by cardiovascular diseases

in deaths during the 31–60 days control period, whereas in deaths that occurred during risk intervals the ranking was reversed with 44% of people with cardiovascular diseases among the deaths in the 3 days risk interval. In regards to type of vaccine, we found that the most frequent vaccine was BNT162b2 in all risk and control intervals, mRNA-1273 was the second most frequent vaccine reaching 36.06 and 43.94% in the 7 and 3 days risk intervals.

There were some differences in the distribution of frail subjects, with more subjects with very high or high frailty in deaths occurred in the 1–3 days risk interval in comparison with deaths occurred during other intervals.

The mortality rate was 2.24 per 100 person-years during the 1–30 days risk interval and was 2.72 per 100 in the 31–60 days control interval (Table 3) with an unadjusted incidence rate ratio (IRR) equal to 0.83 (95% CI: 0.76–0.90, p < 0.0001) (Table 4). Similar IRR (0.75, 95% CI: 0.69–0.82, p < 0.0001) was observed in the sample where all SARS-CoV-2 infections that occurred after vaccination were excluded with rates of 2.04 and 2.56 per 100 person-years in the 1–30 days risk and the 31–60 days control period respectively. As Table 3 shows, for any length of follow-up period the risk interval had lower mortality rate than the 31–60 days control interval.

The adjusted risk of mortality is significantly lower in all risk intervals than in the control intervals (p < 0.001) (Table 4). When replicating the analyses by different strata, the IRR is significantly below 1 in both sexes, in all age groups except for the <65 years old group (30 and 3 days risk interval) and in receivers of Ad26 CoV2-S (calculated only for the 30 and 14 days risk interval) or ChAdOx1-S and mRNA-1273 (3 days risk interval). Similar results were obtained when the analyses were replicated in the +18 population adjusting for the frailty index (Table 1 Supplementary material).

Table 5 shows place and causes of death during the study intervals. During the 31–60 days control interval there was a significantly (p < 0.001) higher proportion of hospital deaths than in the risk intervals and this difference was greater (58.37% vs 30.30%) when comparing the 3 days following vaccination, while the proportion of home deaths was greater in the 3 days risk interval (45.45% vs 22.79%).

As far as causes of death are concerned, there were more deaths for neoplasms and nervous system diseases and fewer for circulatory and respiratory diseases in the control intervals than in the risk intervals. COVID-19-related deaths were higher among events occurred 30 days following vaccination than in the 31–60 days control interval.

4. Discussion

This study assesses whether the days following vaccination for the prevention of COVID-19 are associated with an increase in mortality. We conducted a retrospective evaluation among all vaccinated subjects and found that the days following vaccination were not characterized by an increase in mortality. On the contrary, they were associated with a reduction in mortality in all risk periods. Whether we considered a short-time frame after administration (3, 7 days) or a longer time frame (14, 30 days) the mortality rate was lower than the rate observed one month since vaccination. This finding was replicated for recipients of any approved vaccine, BNT162b2, mRNA-1273, ChAdOx1-S and Ad26 CoV2-S, although with varying degrees of strength and significance.

This finding is in line with previous epidemiological studies [15–17] on mortality associated with vaccines used to prevent COVID-19 in spite of the differences in objectives, study population, follow-up period and other differences in study design. Bardenheier et al. [17] compared vaccinated and unvaccinated

Table 1
Demographic and clinical characteristics of the study population.

	Study population	
	No.	%
Total	717,538	100
Sex		
F	370,813	51.68
M	346,725	48.32
Age group (years)		
0–17	44,455	6.20
18–40	186,386	25.98
41–64	280,965	39.16
65–74	90,690	12.64
75–84	75,623	10.54
>84	39,419	5.49
Citizenship		
Italian	645,600	89.97
Non italian	71,938	10.03
Comorbidities (previous two years)*		
Cardiovascular diseases	50,157	7.69
Tumours	93,942	14.41
Diabetes	50,966	7.82
Hypertension	63,872	9.79
Cerebrovascular diseases	20,417	3.13
Parkinson	9,729	1.49
Dementia	6,632	1.02
Mental health disorders	17,469	2.68
Diseases of the respiratory system	22,522	3.45
Renal failure	9,521	1.46
SARS-CoV-2 infection	4,619	0.64
Frailty class*		
Very low	472,815	72.50
Low	144,401	22.14
Medium	22,320	3.42
High	11,244	1.72
Very high	1,365	0.21
Type of vaccine*		
ChAdOx1-S	23,558	3.28
Ad26 CoV2-S	5,557	0.77
mRNA-1273	260,409	36.30
BNT162b2	427,943	59.65

* Information not available for all.

Table 2
Demographic, clinical characteristics and vaccine administered of deaths occurred during risk and non-risk intervals.

| | Control interval | | Risk interval | | | | | | | |
| | 31–60 days | | 1–30 days | | 1–14 days | | 1–7 days | | 1–3 days | |
Follow up period	No.	%	No.	%	No.	%	No.	%	No.	%
Total	1,015	100	1,152	100	487	100	208	100	66	100
Sex										
Female	533	52.51	615	53.39	269	55.24	121	58.17	35	53.03
Male	482	47.49	537	46.61	218	44.76	87	41.83	31	46.97
Age group (years)										
0–17	0		1	0.09	1	0.21	1	0.48	0	
18–40	8	0.79	8	0.69	6	1.23	3	1.44	1	1.52
41–64	60	5.91	71	6.16	22	4.52	9	4.33	2	3.03
65–74	103	10.15	107	9.29	46	9.45	20	9.62	5	7.58
75–84	282	27.78	323	28.04	134	27.52	60	28.85	20	30.30
>84	562	55.37	642	55.73	278	57.08	115	55.29	38	57.58
Citizenship										
Italian	1,003	98.82	1,142	99.13	482	98.97	204	98.08	65	98.48
Non italian	12	1.18	10	0.87	5	1.03	4	1.92	1	1.52
Civic status										
Single	98	9.70	128	11.18	52	10.74	28	13.59	5	7.69
Married	409	40.50	419	36.59	165	34.09	79	38.35	27	41.54
Widowed	471	46.63	553	48.30	245	50.62	95	46.12	31	47.69
Divorced	32	3.17	45	3.93	22	4.55	4	1.94	2	3.08
Education										
University	52	5.58	59	5.53	23	5.075	9	4.66	1	1.56
High school	125	13.41	130	12.18	60	13.22	30	15.54	11	17.19
Secondary school	285	30.58	355	33.27	147	32.38	61	31.61	16	25.00
Primary school	470	50.43	523	49.02	224	49.34	93	48.19	36	56.25
Comorbidities (previous two years)*										
Cardiovascular diseases	356	35.28	429	37.57	181	37.63	73	35.61	28	43.75
Tumours	372	36.87	374	32.75	159	33.06	67	32.68	24	37.50
Diabetes	224	22.20	281	24.61	120	24.95	58	28.29	17	26.56
Hypertension	340	33.70	355	31.09	152	31.60	65	31.71	21	32.81
Cerebrovascular diseases	232	22.99	246	21.54	100	20.79	47	22.93	14	21.88
Parkinson	105	10.41	97	8.49	38	7.90	19	9.27	2	3.13
Dementia	165	16.35	204	17.86	83	17.26	41	20.00	10	15.63
Mental health disorders	39	3.87	36	3.15	10	2.08	4	1.95	0	
Diseases of the respiratory system	159	15.76	195	17.08	80	16.63	41	20.00	15	23.44
Renal failure	128	12.69	166	14.54	72	14.97	36	17.56	10	15.63
SARS-CoV-2 infection	63	6.24	109	9.46	34	6.98	6	2.88	1	1.52
Frailty class*										
Very low	54	5.35	51	4.47	20	4.16	9	4.39	3	4.69
Low	372	36.87	402	35.20	178	37.01	73	35.61	22	34.38
Medium	286	28.34	334	29.25	132	27.44	56	27.32	13	20.31
High	252	24.98	286	25.04	123	25.57	52	25.37	21	32.81
Very high	45	4.46	69	6.04	28	5.82	15	7.32	5	7.81
Type of vaccine										
ChAdOx1-S	36	3.57	21	1.82	6	1.23	1	0.48	1	1.52
Ad26 CoV2-S	2	0.20	2	0.17	1	0.21	1	0.48	0	
mRNA-1273	267	26.46	336	29.17	158	32.44	75	36.06	29	43.94
BNT162b2	710	70.37	793	68.84	322	66.12	131	62.98	36	54.55

* Information not available for all.

Table 3
Deaths, person-years and mortality rate × 100 during the risk and control intervals, with 95% confidence interval (CI) by follow-up period in all study population and after excluding subjects who had a confirmed SARS-CoV-2 infection after vaccination.

	n. deaths	Person-years	Rate × 100 person-years	95 %CI	
All study population					
Control interval 31–60 days	1,015	37,358	2.72	2.55	2.89
Risk interval 1–30 days	1,152	51,338	2.24	2.12	2.38
1–14 days	487	27,329	1.78	1.63	1.95
1–7 days	208	15,130	1.37	1.19	1.57
1–3 days	66	5,836	1.13	0.87	1.44
After excluding people with a SARS-CoV-2 infection after vaccination					
Control interval 31–60 days	952	37,157	2.56	2.40	2.73
Risk interval 1–30 days	1,043	51,008	2.04	1.92	2.17
1–14 days	453	27,149	1.67	1.52	1.83
1–7 days	202	15,029	1.34	1.17	1.54
1–3 days	65	5,798	1.12	0.87	1.43

Table 4
Incident rate ratio (IRR) and relative 95% confidence interval (CI) by follow-up period and sex, age class and vaccine type and after excluding subjects that had a confirmed SARS-CoV-2 infection after vaccination.

	Population/Subgroup	IRR	95 %CI		p-value
	1–30 days vs 31–60 days				
Unadjusted estimate	Overall	0.83	0.76	0.90	<0.0001
Adjusted estimates*	Overall	0.76	0.70	0.83	0.0001
	Sex				
	Female	0.79	0.70	0.89	0.0001
	Male	0.73	0.64	0.82	<0.0001
	Age group (years)				
	<65$	0.81	0.58	1.12	0.1926
	65–74	0.53	0.40	0.71	<0.0001
	75–84	0.64	0.54	0.76	<0.0001
	>84	0.83	0.74	0.94	0.0024
	Vaccine type				
	ChAdOx1-S	0.30	0.16	0.54	0.0001
	Ad26 CoV2-S	0.58	0.07	4.59	0.6055
	mRNA-1273	0.77	0.65	0.91	0.0018
	BNT162b2	0.76	0.68	0.84	<0.0001
	Excluding SARS-CoV-2 infection	0.75	0.69	0.82	<0.0001
	1–14 days vs 31–44 days				
Unadjusted estimate	Overall	0.63	0.56	0.71	<0.0001
Adjusted estimates*	Overall	0.62	0.55	0.70	<0.0001
	Sex				
	Female	0.67	0.56	0.79	0.0001
	Male	0.57	0.47	0.68	<0.0001
	Age group (years)				
	<65$	0.58	0.35	0.96	0.0357
	65–74	0.44	0.29	0.66	0.0001
	75–84	0.50	0.39	0.64	<0.0001
	>84	0.70	0.60	0.83	<0.0001
	Vaccine type				
	ChAdOx1-S	0.17	0.06	0.45	0.0004
	Ad26 CoV2-S	0.25	0.01	6.84	0.3755
	mRNA-1273	0.67	0.53	0.85	0.0014
	BNT162b2	0.60	0.51	0.70	<0.0001
	Excluding SARS-CoV-2 infection	0.63	0.55	0.72	<0.0001
	1–7 days vs 31–37 days				
Unadjusted estimate	Overall	0.50	0.42	0.60	<0.0001
Adjusted estimates*	Overall	0.50	0.42	0.60	<0.0001
	Sex				
	Female	0.60	0.47	0.76	0.0001
	Male	0.41	0.32	0.54	<0.0001
	Age group (years)				
	<65$	0.44	0.22	0.88	0.0204
	65–74	0.41	0.22	0.74	0.0031
	75–84	0.38	0.27	0.53	<0.0001
	>84	0.59	0.46	0.76	<0.0001
	Vaccine type				
	ChAdOx1-S	0.10	0.01	0.81	0.0347
	Ad26 CoV2-S	0.10	0.01	0.81	0.0347
	mRNA-1273	0.60	0.43	0.83	0.0033
	BNT162b2	0.46	0.37	0.58	<0.0001
	Excluding SARS-CoV-2 infection	0.54	0.45	0.65	<0.0001
	1–3 days vs 31–33 days				
Unadjusted estimate	Overall	0.41	0.29	0.56	<0.0001
Adjusted estimates*	Overall	0.38	0.28	0.52	<0.0001
	Sex				
	Female	0.44	0.29	0.68	0.0002
	Male	0.34	0.22	0.52	<0.0001
	Age group (years)				
	<65$	0.34	0.09	1.38	0.1310
	65–74	0.24	0.08	0.71	0.0094
	75–84	0.23	0.13	0.40	<0.0001
	>84	0.53	0.35	0.81	0.0036
	Vaccine type				
	ChAdOx1-S	0.13	0.02	1.10	0.0676
	Ad26 CoV2-S	0.13	0.02	1.10	0.0676
	mRNA-1273	0.76	0.43	1.33	0.3562
	BNT162b2	0.29	0.19	0.43	<0.0001
	Excluding SARS-CoV-2 infection	0.43	0.31	0.59	<0.0001

* Adjusted for age, day of week and period of vaccination.
$ Age class 18–40 and 41–64 are grouped to increase the number of events.

Table 5
Place and causes of deaths by control and risk intervals.

	Control interval		Risk interval							
	31–60 days		1–30 days		1–14 days		1–7 days		1–3 days	
	No.	%	No.	%	No.	%	No.	%	No.	%
Total	1,015	100	1,152	100	487	100	208	100	66	100
Place of death										
Home	230	22.79	332	28.82	179	36.76	84	40.38	30	45.45
Hospital	589	58.37	590	51.22	197	40.45	73	35.10	20	30.30
Nursing home	154	15.26	159	13.80	80	16.43	38	18.27	12	18.18
Other	42	4.16	71	6.16	31	6.37	13	6.25	4	6.06
Causes of deaths										
Natural causes	956	94.75	1,094	94.97	460	94.46	199	95.67	63	95.45
Certain infectious and parasitic diseases	37	3.67	29	2.52	13	2.67	7	3.37	1	1.52
COVID-19	42	4.16	97	8.42	27	5.54	5	2.40	0	
Neoplasms	245	24.28	199	17.27	75	15.40	29	13.94	9	13.64
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	8	0.79	6	0.52	2	0.41	1	0.48	1	1.52
Endocrine, nutritional, and metabolic diseases	36	3.57	53	4.60	21	4.31	13	6.25	4	6.06
Mental and behavioural disorders	46	4.56	54	4.69	22	4.52	9	4.33	4	6.06
Diseases of the nervous system	42	4.16	28	2.43	13	2.67	7	3.37	1	1.52
Diseases of the circulatory system	312	30.92	402	34.9	187	38.4	79	37.98	24	36.36
Diseases of the respiratory system	83	8.23	105	9.11	40	8.21	20	9.62	13	19.70
Diseases of the digestive system	35	3.47	45	3.91	21	4.31	9	4.33	1	1.52
Diseases of the skin and subcutaneous tissue	4	0.40	6	0.52	2	0.41	0		0	
Diseases of the musculoskeletal system and connective tissue	3	0.30	6	0.52	2	0.41	2	0.96	0	
Diseases of the genitourinary system	45	4.46	39	3.39	21	4.31	7	3.37	2	3.03
Congenital malformations, deformations and chromosomal abnormalities	1	0.10	0		0		0		0	
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	17	1.68	25	2.17	14	2.87	11	5.29	3	4.55
External causes of morbidity and mortality	59	5.85	58	5.03	27	5.54	9	4.33	3	4.55

residents of nursing homes and monitored deaths and other adverse events for 7 days and found lower mortality rates in vaccinated. Xu et al. [16] conducted a cohort study and analysed non-COVID related deaths during a 7 months follow up period and also reported lower rates of mortality between vaccinated and did not find major safety problems following the first or second dose of the vaccines. Lv et al. [15] reported on 55 deaths following vaccination noting that the majority of the reported deaths were in people aged 85 and older with serious underlying health conditions.

As already remarked by other authors [16] it is unlikely that the vaccine has a protective effect, especially when we excluded COVID-19 related events. Rather, the lower mortality observed by other authors [16] was ascribed by a healthy vaccine effect or, as an alternative hypothesis, by healthier risk behaviours adopted by vaccinated than non-vaccinated in studies with both vaccinated and unvaccinated groups.

Although we included only vaccinated subjects, our finding can also be ascribed by the healthy vaccine effect based on selective prescription [19]. It is unlikely that people who were in very unstable conditions and that were prone to death received a dose of vaccination. Nevertheless, the vaccine was administered also to very old and frail people that were sufficiently well at the moment of the administration but that might have had a rapid decline in health in the time frame of a month.

An important secondary finding of our study is that deaths occurred in the days immediately following vaccination occurred more often at home and for circulatory diseases than in hospital or for neoplasms and neurological diseases. This finding corroborates the healthy vaccine effect suggesting that hospitalized patients in terminal phase were excluded from the vaccination. The same did not happen for patients with circulatory disease whose outcome is by the very nature of this disease, more sudden and less predictable. We observe also that the lower mortality risk is present in all strata, but it does not achieve significance in younger groups or with Ad26 CoV2-S or ChAdOx1-S where the number of events is very small nor in the 3 days following

mRNA-1273 which was mainly administered at home and in nursing home residents where more subjects in unstable conditions might have received the vaccine.

During the post-market surveillance a link was highlighted between COVID-19 vaccines and some severe, adverse events, in particular: thrombosis, thrombocytopenia and transverse myelitis following ChAdOx1-S [20,21] anaphylaxis following mRna vaccines, myocarditis and pericarditis in younger [10,22] also following mRNA vaccines. In addition, in some post-mortem investigation a causative relationship between vaccines and deaths in the 72 h after receiving the vaccine has been observed [8,13]. These events are nevertheless very rare and so far there is a general consensus that the benefits of vaccination far outweigh the potential risks [10,11]. Fatal events occur at any time and do occur also in temporal association with preventive measures. In this sense by studying all deaths after vaccination we did not observe any negative impact on mortality in the short-term.

5. Strengths and limitations

This was a large population-based study encompassing a period of one year where we looked at multiple timeframe after vaccination and thus including potential deaths for anaphylactic reactions that may occur within a short delay, but also for myocarditis, pericarditis and thrombotic complications that can occur two weeks later [8,13]. In addition, as we adopted a risk interval approach we did not have to compare vaccinated with unvaccinated that are expected to be very different and as such introduce bias in the results. Another strength of the study was the availability of the causes of deaths which gave us the opportunity to provide a deep insight into the main findings of the study.

This study has several limitations that should be taken into account when interpreting the results. One of the main limits of the study is that possible longer-term death associated with vaccination were not detected. In addition, as our goal was to study

short-term mortality associated with vaccination, some events that occurred 30 days after vaccination (the control interval) might have a relationship with the vaccine. Other study design with longer follow-up should be conducted to explore long-term adverse events and long-term mortality of COVID-19 vaccines.

Another limit of the study is the small size of some subgroups which is not sufficient to detect significant differences. By observing the main clinical characteristics of the participants, we did not find important differences when comparing deaths during the risk vs the control interval.

By comprising >700,000 vaccinated subjects of all ages and analysing all fatal events occurred after the administration of COVID-19 vaccines, we did not find any negative impact in the short-term mortality during the first year of the campaign, a finding that may contribute to reducing hesitancy towards these vaccines.

All authors attest they meet the ICMJE criteria for authorship.

Data availability

Data will be made available on reasonable request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.08.039.

References

[1] Li Y, Tenchov R, Smoot J, Liu C, Watkins S, Zhou Q. A comprehensive review of the global efforts on COVID-19 vaccine development. ACS Cent Sci 2021;7:512–33. https://doi.org/10.1021/acscentsci.1c00120.

[2] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384 (5):403–16.

[3] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383 (27):2603–15.

[4] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet Lond Engl 2021;397(10269):99–111.

[5] Sadoff J, Gray G, Vandebosch An, Cárdenas V, Shukarev G, Grinsztejn B, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med 2021;384(23):2187–201.

[6] Solís Arce JS, Warren SS, Meriggi NF, Scacco A, McMurry N, Voors M, et al. COVID-19 vaccine acceptance and hesitancy in low- and middle-income countries. Nat Med 2021;27(8):1385–94.

[7] Schwarzinger M, Watson V, Arwidson P, Alla F, Luchini S. COVID-19 vaccine hesitancy in a representative working-age population in France: a survey experiment based on vaccine characteristics. Lancet Public Health 2021;6: e210–21. https://doi.org/10.1016/S2468-2667(21)00012-8.

[8] Yeo A, Kuek B, Lau M, Tan SR, Chan S. Post COVID-19 vaccine deaths - Singapore's early experience. Forensic Sci Int 2022;332:111199. https://doi.org/10.1016/j.forsciint.2022.111199.

[9] AIFA. Rapporto annuale sulla sicurezza dei vaccini anti-COVID-19 (27/12/2020-26/12/2021) n.d. <https://aifa.gov.it/farmacovigilanza-vaccini-covid-19> [accessed February 13, 2022].

[10] EMA. Safety of COVID-19 vaccines. Eur Med Agency; 2021. <https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/safety-covid-19-vaccines> [accessed February 22, 2022].

[11] Rosenblum HG, Gee J, Liu R, Marquez PL, Zhang B, Strid P, et al. Safety of mRNA vaccines administered during the initial 6 months of the US COVID-19 vaccination programme: an observational study of reports to the vaccine adverse event reporting system and v-safe. Lancet Infect Dis 2022;22 (6):802–12.

[12] Torjesen I. Covid-19: Norway investigates 23 deaths in frail elderly patients after vaccination. BMJ 2021;372:. https://doi.org/10.1136/bmj.n149n149.

[13] Sessa F, Salerno M, Esposito M, Di Nunno N, Zamboni P, Pomara C. Autopsy findings and causality relationship between death and COVID-19 vaccination: a systematic review. J Clin Med 2021;10:5876. https://doi.org/10.3390/jcm10245876.

[14] CDC. COVID-19 Vaccination. Cent Dis Control Prev; 2020. <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html> [accessed March 29, 2022].

[15] Lv G, Yuan J, Xiong X, Li M. Mortality Rate and Characteristics of Deaths Following COVID-19 Vaccination. Front Med 2021;8:670370. https://doi.org/10.3389/fmed.2021.670370.

[16] Xu S, Huang R, Sy LS, Glenn SC, Ryan DS, Morrissette K, et al. COVID-19 vaccination and non-COVID-19 mortality risk - seven integrated health care organizations, United States, December 14, 2020-July 31, 2021. MMWR Morb Mortal Wkly Rep 2021;70(43):1520–4.

[17] Bardenheier BH, Gravenstein S, Blackman C, Gutman R, Sarkar IN, Feifer RA, et al. Adverse events following mRNA SARS-CoV-2 vaccination among U.S. nursing home residents. Vaccine 2021;39(29):3844–51.

[18] Pandolfi P, Collina N, Marzaroli P, Stivanello E, Musti MA, Giansante C, et al. Development of a predictive model of death or urgent hospitalization to identify frail elderly. Epidemiol Prev 2016;40:395–403. https://doi.org/10.19191/EP16.6.P395.119.

[19] Shrank WH, Patrick AR, Alan BM. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. J Gen Int Med 2011;26:546–50. https://doi.org/10.1007/s11606-010-1609-1.

[20] Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384(22):2124–30.

[21] Silva GF, Silva CF, Oliveira RENdN, Silva FWD, Baptista JPR, Loz SH, et al. Transverse myelitis and coronavirus disease 2019 vaccine: a temporal association. Clin Exp Neuroim 2022;13(2):75–9.

[22] Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med 2022;28(2):410–22.