

Relative effectiveness of a 2nd booster dose of COVID-19 mRNA vaccine up to four months post administration in individuals aged 80 years or more in Italy: A retrospective matched cohort study



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ABSTRACT

Several countries started a 2nd booster COVID-19 vaccination campaign targeting the elderly population, but evidence around its effectiveness is still scarce. This study aims to estimate the relative effectiveness of a 2nd booster dose of COVID-19 mRNA vaccine in the population aged ≥ 80 years in Italy, during predominant circulation of the Omicron BA.2 and BA.5 subvariants.

We linked routine data from the national vaccination registry and the COVID-19 surveillance system. On each day between 11 April and 6 August 2022, we matched 1:1, according to several demographic and clinical characteristics, individuals who received the 2nd booster vaccine dose with individuals who received the 1st booster vaccine dose at least 120 days earlier. We used the Kaplan-Meier method to compare the risks of SARS-CoV-2 infection and severe COVID-19 (hospitalisation or death) between the two groups, calculating the relative vaccine effectiveness (RVE) as $(1 - \text{risk ratio}) \times 100$.

Based on the analysis of 831,555 matched pairs, we found that a 2nd booster dose of mRNA vaccine, 14–118 days post administration, was moderately effective in preventing SARS-CoV-2 infection compared to a 1st booster dose administered at least 120 days earlier [14.3 %, 95 % confidence interval (CI): 2.2–20.2]. RVE decreased from 28.5 % (95 % CI: 24.7–32.1) in the time-interval 14–28 days to 7.6 % (95 % CI: –14.1 to 18.3) in the time-interval 56–118 days. However, RVE against severe COVID-19 was higher (34.0 %, 95 % CI: 23.4–42.7), decreasing from 43.2 % (95 % CI: 30.6–54.9) to 27.2 % (95 % CI: 8.3–42.9) over the same time span.

Although RVE against SARS-CoV-2 infection was much reduced 2–4 months after a 2nd booster dose, RVE against severe COVID-19 was about 30 %, even during prevalent circulation of the Omicron BA.5 subvariant. The cost-benefit of a 3rd booster dose for the elderly people who received the 2nd booster dose at least four months earlier should be carefully evaluated.

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Abbreviations: RVE, relative vaccine effectiveness; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; mRNA, messenger ribonucleic acid; LTCF, long-term care facility; PCR, polymerase chain reaction; ECDC, European centre for disease prevention and control; WHO, World Health Organization; IQR, interquartile range; RR, risk ratio; RD, risk difference; RRR, relative risk reduction; CI, confidence interval; RHR, relative hazard reduction.

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1. Introduction

The rising number of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections associated with the rapid spread of the Omicron (B.1.1.529) variant, alongside evidence of waning effectiveness few months after a first booster dose of coronavirus disease 2019 (COVID-19) vaccine [1], led several countries to start a second booster vaccination campaign targeting the elderly population and other high-risk groups.

In Italy, a second booster vaccination campaign against COVID-19 targeting all persons aged ≥ 80 years (regardless of health status), persons aged ≥ 60 years presenting health-risk conditions, and residents in long-term care facilities (LTCF) started on 11 April 2022 [2]. The second booster vaccination campaign was subsequently extended, on 11 July 2022, to all persons aged 60–79 years, regardless of health status, and to persons aged ≥ 12 years presenting health-risk conditions [3]. The administration of the second booster dose was recommended at least four months after the administration of the first booster dose or a prior infection using messenger ribonucleic acid (mRNA) vaccines [i.e., BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna)].

As of 4 September 2022, a total of 2,305,053 people received a second booster vaccine dose. Of these, more than half were elderly people aged ≥ 80 years (1,318,583; 57.2 %) [4].

There is limited evidence around the effectiveness of a 2nd booster vaccine dose and comparability across the published studies is difficult due to methodological heterogeneity (e.g., different study populations) [5–13]. The few studies focusing on the general elderly population were all conducted in Israel, during predominance of the Omicron BA.1 and BA.2 subvariants, and were based on a relatively short follow-up time, ranging from 2 to 10 weeks after the administration of the second booster vaccine dose [7–10].

This study aims to evaluate the relative effectiveness of a second booster dose of mRNA vaccine up to 17 weeks post administration, as compared to a first booster dose given at least 120 days earlier, in the elderly population aged ≥ 80 years in Italy, during an epidemic phase characterized by predominance of the Omicron BA.2 and BA.5 subvariants.

2. Material and methods

2.1. Data sources and study design

Using the individual tax code as key variable, we linked data on vaccinated persons from the Italian National Vaccination Registry (held by the Ministry of Health) [14] with data on notified laboratory-confirmed cases of SARS-CoV-2 infection from the National COVID-19 Integrated Surveillance System (coordinated by the Istituto Superiore di Sanità, namely the Italian National Institute of Health) [15]. The National Vaccination Registry includes information on demographic and clinical characteristics for all individuals who received at least one dose of a COVID-19 vaccine in Italy, as well as the date and type of vaccine for each administered dose. The National COVID-19 Surveillance System collects data on all notified cases of SARS-CoV-2 infection who were laboratory-confirmed through a polymerase chain reaction (PCR) assay or, since 15 January 2021, through an antigenic test performed in medically attended facilities (pharmacies and private/public health centres). It includes information on date of testing and COVID-19 related clinical outcomes (e.g., hospitalisation and death).

We conducted a matched retrospective cohort study, emulating a clinical trial [16,17], to compare times to SARS-CoV-2 infection and to severe COVID-19 between persons aged ≥ 80 years who had received the 2nd booster dose of an mRNA vaccine in Italy and those who had received only the 1st booster dose at least 120 days earlier. The study started on 11 April 2022 (starting date of the second booster vaccination campaign targeting all persons aged ≥ 80 years in Italy) [2], when the Omicron BA.2 variant was predominant in Italy (Fig. 1) [18]. It ended on 7 August 2022, when the Omicron BA.5 variant was predominant [19], to ascertain SARS-CoV-2 infections leading to hospitalisation or death within 28 days since the date of testing positive, up to 4 September 2022. We used data extracted from both sources on 7 September 2022, thus

accounting for at least 3 days of possible notification delay for the last event of interest.

No information on possible deaths occurred for causes unrelated to COVID-19 was available from these data sources. Therefore, based on the life tables by region, age, and sex for the year 2019 published by the Italian Institute of Statistics [20], assuming a uniform distribution of deaths over the year, we imputed the expected date of death of vaccinated persons who were not diagnosed with infection during the study period (see Supplementary Method S1 for more details).

2.2. Selection of the study sample

We initially selected from the National Vaccination Registry all individuals aged ≥ 80 years at the start of the study (11 April 2022) who had received at least one vaccine dose before the end of the study (7 August 2022) (Fig. 2). We then excluded the following groups:

- persons who did not receive the 1st booster dose,
- persons who died before the start of the study,
- persons who received the 1st booster dose before 27 September 2021 (starting date of the 1st booster vaccination campaign for persons aged ≥ 80 years, regardless of frailty status or other high-risk conditions [21]),
- persons who received the 1st booster dose after 12 December 2021 (less than 120 days before the starting date of the study),
- persons who received the 2nd booster dose before the starting date of the study (coinciding with the starting date of the 2nd booster vaccination campaign for persons aged ≥ 80 years, regardless of immunodeficiency status [2]),
- persons who tested positive for SARS-CoV-2 infection less than 120 days before the study starting date (not eligible to receive a 2nd booster dose on that date),
- persons with missing or inconsistent information (less than 1%).

The remaining eligible individuals were classified as having received a 2nd booster dose before the end of the study on 7 August 2022 (2nd booster group) or having received only the 1st booster dose (1st booster group). For each day from 11 April to 6 August 2022, we matched 1:1 (with replacement) any individual who had received the 2nd booster dose on that day with a randomly selected individual who, on the same day, was alive and was not tested positive for SARS-CoV-2 infection earlier during the study period (including individuals in the 2nd booster group who had not yet received the 2nd booster dose by that day). Matching was based on sex, exact age measured in years (up to 95 and then grouping ≥ 95 years), country of birth (Italy vs other countries), geographical area where vaccination took place (19 regions and 2 autonomous provinces), presence/absence of high-risk conditions (i.e., residence in LTCFs or at least one of the health-risk conditions listed in Table S1 of the supplementary material), time since prior infection (i.e., no prior infection, exact number of days from 120 to 365, and then grouping greater than 365 days), week of administration of the 1st booster dose, and type of vaccine used for administration of the 1st booster dose (i.e., BNT162b2 or mRNA-1273).

2.3. Outcomes and exposure

We compared the time to SARS-CoV-2 infection of any severity (symptomatic or asymptomatic), and the time to infection with complications leading to hospitalisation or death within 28 days since testing positive (severe COVID-19) between individuals aged ≥ 80 years who received a second booster dose of mRNA vac-

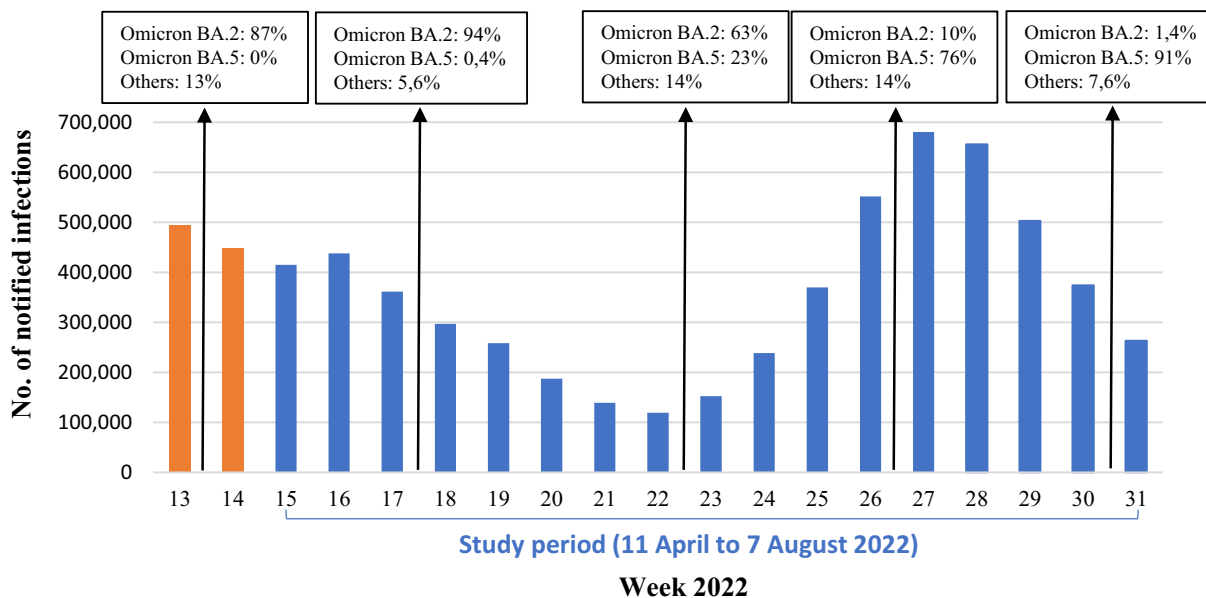


Fig. 1. Epidemic curve of notified cases of SARS-CoV-2 infections alongside estimates of the Omicron subvariants prevalence at different calendar weeks.

cine (exposed group) and those who received the first booster dose at least 120 days earlier (unexposed group).

As per laboratory criteria for case definition from the European Centre for Disease Prevention and Control (ECDC) [22], cases of SARS-CoV-2 infections notified to the surveillance system include those laboratory-confirmed by PCR (30.4 % of cases in the study sample) or, since 15 January 2021, also those tested positive through an antigenic test (69.6 % of cases in the study sample). Of these cases, those who were reported to have been hospitalized or died within four weeks since infection for COVID-19 related causes were classified as severe cases. According to Italian guidelines, based on indications from the World Health Organization (WHO) [23], a death was considered as related to COVID-19 if occurred in the presence of a clinical and instrumental picture suggestive of COVID-19, the absence of a clear cause of death different from COVID-19 (e.g., road accident), and the absence of a complete clinical recovery from the disease. Similarly, the surveillance system foresees and is expected to record only hospitalisations directly attributable to SARS-CoV-2 infection and not due to other causes.

2.4. Statistical analysis

We described the baseline characteristics of the matched pairs and those of the overall eligible population from which they were drawn using counts with percentages and median with interquartile range (IQR).

In the time-to-event analyses (time to SARS-CoV-2 infection and time to severe COVID-19), for each matched pair, the follow-up started on the date of administration of the 2nd booster dose to the member of the exposed group. It ended on the date of testing positive for SARS-CoV-2 infection, date of death, date when the member of the unexposed group received a 2nd booster dose of vaccine (with concurrent censoring of the paired member of the exposed group), or 7 August 2022 (end of the study), whichever came first. The follow-up time was calculated as the number of days elapsed from the starting date to the ending date.

We evaluated differences in the cumulative incidence of SARS-CoV-2 infection and severe COVID-19 over time between the 1st booster group and the 2nd booster group by plotting the Kaplan-

Meier failure curves and testing differences through the log-rank test.

After selection of the matched pairs with both members still under observation 14 days after the start of follow-up, we used the Kaplan-Meier estimator to compare the risks of SARS-CoV-2 infection and severe COVID-19 at 118 days between the 1st booster group and the 2nd booster group through risk ratios (RR) and risk differences (RD). The effectiveness of the 2nd booster dose of vaccine relative to the 1st booster dose was calculated as relative risk reduction [RRR=(1-RR)X100].

The same analysis was conducted to estimate the RRRs and RDs at different time-intervals (i.e., 14–28, 28–56, and 56–118 days since the start of follow-up), including only matched pairs still under observation at the beginning of each of them. Estimates of RRR and RD were presented together with 95 % confidence interval (CI) based on percentiles derived from non-parametric bootstrapping with 1,000 sampling repetitions. CIs do not account for multiplicity and should therefore not be used to evaluate statistical significance of differences between time-intervals.

Finally, we conducted two sensitivity analyses. First, assuming that some degree of protection induced by a 2nd booster dose might already be present 7 days after its administration, we repeated the primary analysis including the matched pairs who were still under observation 7 days after the start of follow-up. Second, we used Cox proportional hazard models to estimate the relative hazard reduction (RHR) for SARS-CoV-2 infection and severe COVID-19 at different time-intervals, after verification of the proportional hazard assumption within each of them through testing based on Schoenfeld residuals. Only matched pairs still under observation at the beginning of each time-interval were considered.

The analyses were performed using Stata/MP version 17.0 (StataCorp LLC, Texas, USA).

2.5. Ethics

This study, based on routinely collected data, was not submitted for approval to an ethical committee because the dissemination of COVID-19 surveillance data was authorized by Decree Law number 24 on 24 March 2022 (article 13). Because of the retrospective design and the large size of the population under study, in accor-

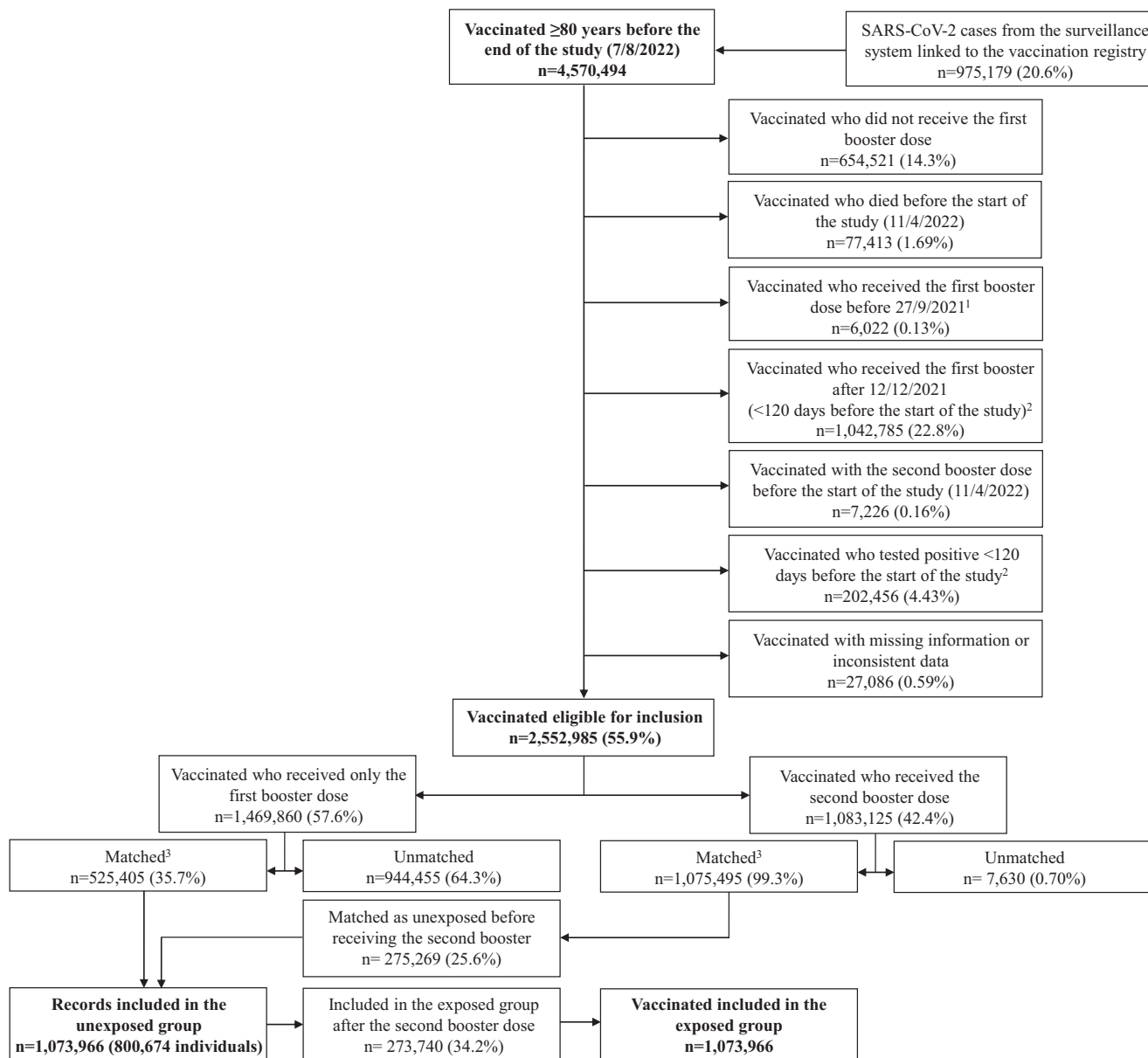


Fig. 2. Selection of the individuals included in the study. ¹ Starting date of the 1st booster vaccination campaign for persons ≥ 80 years, regardless of frailty status and other high-risk conditions. ² Not eligible to receive a second booster dose of vaccine on 11 April 2022 (starting date of the study). ³ Matching by sex, exact age (up to 95 and then grouping ≥ 95 years), country of birth (Italy vs other countries), region where vaccination took place (19 regions and 2 autonomous provinces), presence/absence of high-risk conditions (i.e., residence in LTCF residents or at least one of the health-risk conditions listed in Table S1 of the supplementary appendix), time from prior infection (i.e., no infection, exact number of days up to 365, and then grouping > 365 days), week of administration of the 1st booster dose, type of the 1st booster vaccine dose (i.e., BNT16b2 or mRNA-1273).

dance with the Authorization n. 9 released by the Italian data protection authority on 15 December 2016, the individual informed consent was not requested for the conduction of this study.

3. Results

Among the 4,570,494 persons aged ≥ 80 years who received at least one dose of vaccine by 7 August 2022, a total of 2,017,509 (44.1 %) were not eligible for inclusion, 27,086 (0.59 %) because of missing or inconsistent data (Fig. 2). Of the 2,552,985 eligible individuals, 1,083,125 (42.4 %) were in the 2nd booster group and 1,469,860 (57.6 %) in the 1st booster group. Among the eligible individuals in the 2nd booster group, 275,269 (25.6 %) were matched as unexposed before receiving the 2nd booster dose,

and 1,073,966 (99.2 %) were successfully matched with an unexposed individual and included in the final exposure group. Of the 1,073,966 records included in the unexposed group (1st booster group), 800,674 (74.6 %) were unique individuals. The median follow-up time was 45 days (IQR: 17–80), ranging from 1 to 118 days.

The baseline characteristics of the matched pairs were similar to those of the eligible population from which they were drawn, except for the geographical macroarea where vaccination took place [increased proportion of vaccination in northern Italy in the matched pairs (62.6 %) compared to the eligible individuals who only received the 1st booster dose (46.5 %)] and the number of weeks elapsed from the administration of the 1st booster dose and the starting date of the study [the 1st booster dose was administered earlier in the matched pairs (median number of weeks = 23,

IQR: 21–25) compared to the eligible individuals who only received the 1st dose (median number of weeks = 21, IQR: 19–23)] (Table 1).

The Kaplan-Meier failure curves presented in Fig. 3 show significant differences between the 1st booster group and the 2nd booster group at any time during follow-up (p less than 0.001). Overall, among the 831,555 matched pairs still at risk on day 14, the RRR for SARS-CoV-2 infection in the 2nd booster group compared to the 1st booster group in the time-interval 14–118 days was 14.3 % (95 % CI: 2.2 to 20.2) with RD = 147 per 10,000 (95 % CI: 23 to 212), while the RRR for severe COVID-19 was 34.0 % (95 % CI: 23.4 to 42.7) with RD = 25 per 10,000 (95 % CI: 16 to 34) (Table2).

The relative vaccine effectiveness against SARS-CoV-2 infection in the 2nd booster group compared to the 1st booster group decreased over time from 28.5 % (95 % CI: 24.7 to 32.1) in the time-interval 14–28 days to 7.6 % (95 % CI: –14.1 to 18.3) in the time-interval 56–118 days after the administration of the 2nd booster dose, while the relative effectiveness against severe COVID-19 decreased from 43.2 % (95 % CI: 30.6 to 54.9) in the time-interval 14–28 days to 27.2 % (95 % CI: 8.3 to 42.9) in the time-interval 56–118 days after the administration of the 2nd booster dose) (Table2).

The sensitivity analysis conducted starting the follow-up from day 7 after the 2nd booster dose administration showed similar results, with RRRs for SARS-CoV-2 infection and severe COVID-19

in the time-interval 14–118 days of 14.8 % (95 % CI: 3.1 to 20.5) and 34.9 % (95 % CI: 25.4 to 43.3), respectively (Table 2). Finally, the analysis based on Cox proportional hazard models and estimating RHRs at different time intervals also showed estimates and trends in line with those observed in the primary analysis, except RHR for SARS-CoV-2 infection in the time-interval 56–118 days, found to be 14–21 % compared to 8 % in the primary analysis (Fig. 4).

4. Discussion

We found that in Italy, among persons aged 80 years or more, a 2nd booster dose of mRNA vaccine was moderately effective in preventing SARS-CoV-2 infection in the time-interval 14–118 days post administration as compared to a 1st booster dose administered at least 120 days earlier (14 %, 95 % CI: 2 to 20). Relative effectiveness against infection was found to decrease over the four-months follow-up period, showing no additional protection 56–118 days post administration (8 %, 95 % CI: –14 to 18), a time-interval almost always falling within a calendar period where the Omicron BA.5 subvariant was prevalent in Italy. However, relative effectiveness against severe COVID-19 in the whole follow-up period was higher (34 %, 95 % CI: 23 to 43), decreasing to 27 % (95 % CI: 8 to 43) in the time-interval 56–118 days post administration. Estimates of RDs suggest that a 2nd booster dose of mRNA vaccine

Table 1
Baseline characteristics of the matched pairs and eligible population.

	Matched pairs (n = 1,073,966) ¹		Eligible population First booster only (n = 1,469,860)		Second booster (n = 1,083,125)		Overall (n = 2,552,985)	
	n	(%)	n	(%)	n	(%)	n	(%)
Sex								
Female	612,488	(57.0)	893,064	(60.8)	617,318	(57.0)	1,510,382	(59.2)
Male	461,478	(43.0)	576,796	(39.2)	465,807	(43.0)	1,042,603	(40.8)
Age								
80–84 years	551,939	(51.4)	768,924	(52.3)	555,483	(51.3)	1,324,407	(51.9)
85–89 years	339,637	(31.6)	456,726	(31.1)	342,564	(31.6)	799,290	(31.3)
90–94 years	146,621	(13.7)	193,670	(13.2)	148,813	(13.7)	342,483	(13.4)
≥95 years	35,769	(3.3)	50,540	(3.4)	36,265	(3.3)	86,805	(3.4)
Median (IQR)	84	(82–88)	84	(82–88)	84	(82–88)	84	(82–88)
Country of birth								
Italian-born	1,057,510	(98.5)	1,446,697	(98.4)	1,064,477	(98.3)	2,511,174	(98.4)
Foreign-born	16,456	(1.5)	23,163	(1.6)	18,648	(1.7)	41,811	(1.6)
Geographical macroarea								
North-West	418,672	(39.0)	394,166	(26.8)	421,701	(38.9)	815,867	(32.0)
North-East	253,591	(23.6)	290,188	(19.7)	255,942	(23.6)	546,130	(21.4)
Centre	224,513	(20.9)	355,065	(24.2)	226,228	(20.9)	581,293	(22.8)
South and Islands	177,190	(16.5)	430,441	(29.3)	179,254	(16.5)	609,695	(23.9)
High-risk group²								
No	976,993	(91.0)	1,321,065	(89.9)	982,568	(90.7)	2,303,633	(90.2)
Yes	96,973	(9.0)	148,795	(10.1)	100,557	(9.3)	249,352	(9.8)
Weeks since 1st booster								
18–21	326,151	(30.4)	808,525	(55.0)	329,280	(30.4)	1,137,805	(44.6)
22–25	547,328	(51.0)	543,187	(37.0)	551,000	(50.9)	1,094,187	(42.9)
26–28	200,487	(18.7)	118,148	(8.0)	202,845	(18.7)	320,993	(12.6)
Median (IQR)	23	(21–25)	21	(19–23)	23	(21–25)	22	(20–24)
Prior infection								
No	1,045,596	(97.4)	1,437,967	(97.8)	1,049,644	(96.9)	2,487,611	(97.4)
Yes	28,370	(2.6)	31,893	(2.2)	33,481	(3.1)	65,374	(2.6)
Median number of days (IQR) ³	525	(500–721)	514	(466–697)	521	(490–719)	517	(481–714)
1st booster vaccine								
BNT16b2	924,612	(86.1)	1,192,266	(81.1)	930,915	(85.9)	2,123,181	(83.2)
mRNA-1273	149,354	(13.9)	277,594	(18.9)	152,210	(14.1)	429,804	(16.8)
2nd booster vaccine								
BNT16b2	860,816	(80.2)	NA		868,272	(80.2)	868,272	(80.2)
mRNA-1273	213,150	(19.8)	NA		214,853	(19.8)	214,853	(19.8)

IQR, interquartile range; NA, not applicable.

¹ 1,073,966 records comprising 800,674 (74.6%) unique individuals in the 1st booster group.

² Including residents in long term care facilities and individuals with health risk conditions.

³ Among individuals who tested positive for SARS-CoV-2 infection more than 120 days prior the start of follow-up.

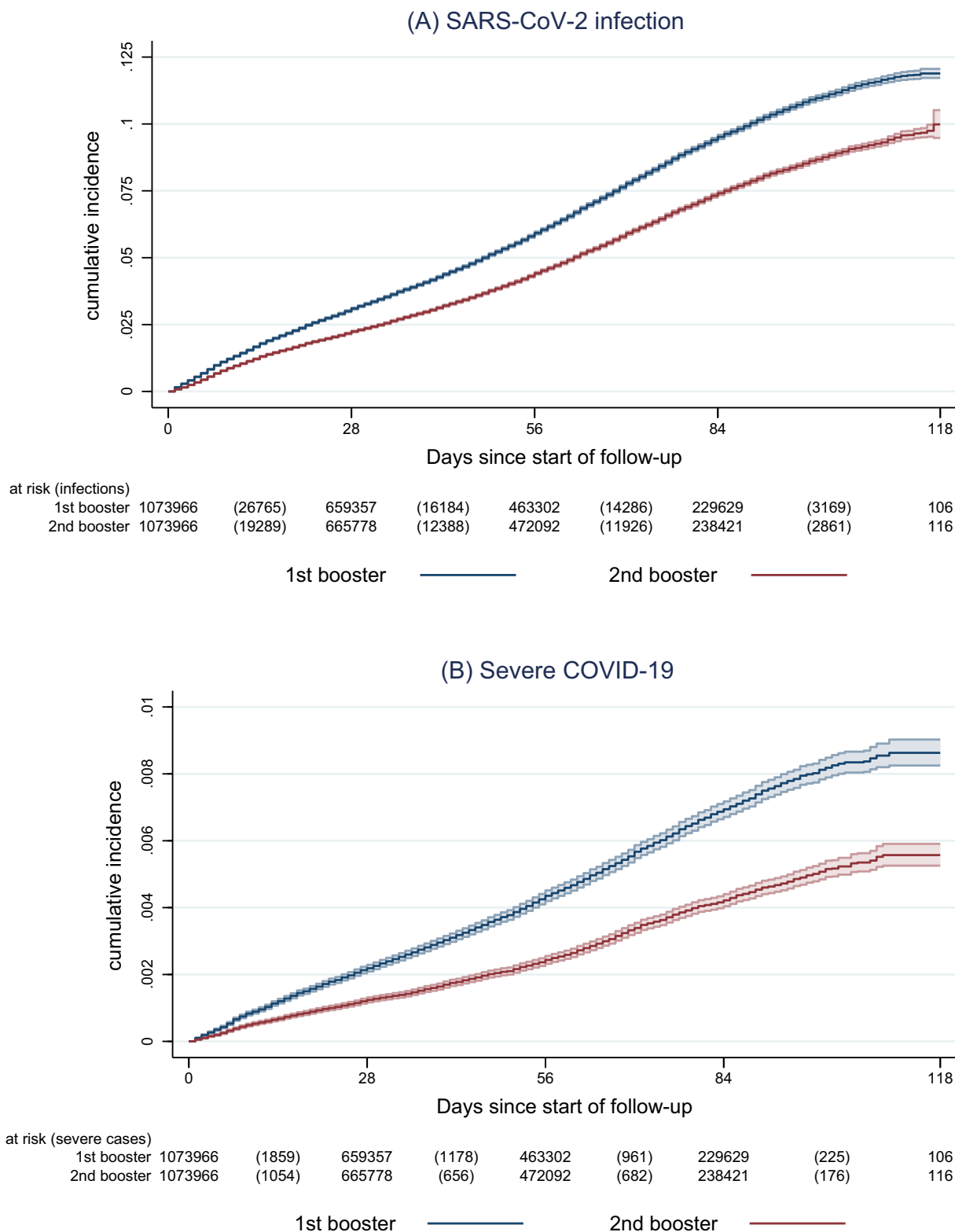


Fig. 3. Cumulative incidence of SARS-CoV-2 infection and severe COVID-19 by booster group. Shaded areas indicate the 95% confidence intervals.

averted 431 cases of SARS-CoV-2 infection and 73 cases of severe COVID-19 per 100,000 individuals in a month during the whole study period. These estimates, especially those for the risk of SARS-CoV-2 infection, appear reduced in the time-interval 56–118 days post administration of the 2nd booster dose (241 cases of SARS-CoV-2 infection and 59 cases of severe COVID-19

averted per 100,000 individuals in a month), as a result of the decrease in relative vaccine effectiveness, rather than a decrease in the incidence of infection.

It is worthwhile to note that, as in the other studies focussing on this topic [5–13], we estimated the relative effectiveness of a 2nd booster dose as compared to a 1st booster dose at the time when

Table 2
Relative risk reduction for SARS-CoV-2 infection following the administration of a second booster vaccine dose.

Severe COVID-19												
SARS-CoV-2 infection						Severe COVID-19						
First booster			Second booster			Relative risk reduction (RRR)			Risk difference (RD)			
No.	risk per 10,000		No.	risk per 10,000		%	(95 % CI)	No.	risk per 10,000		(95 % CI)	
Primary analysis (including the 831,555 matched pairs still at risk on day 14)												
Overall (14–118 days)¹	42,598	1028.0	33,361	881.4	14.3	(2.2 to 20.2)	147	(23 to 212)	3035	74.2	1881	48.9
14–28 days	9896	132.9	7066	94.9	28.5	(24.7 to 32.1)	38	(32 to 44)	735	9.9	417	5.6
28–56 days	15,856	291.1	12,153	223.8	23.1	(20.0 to 26.1)	67	(57 to 77)	1165	21.6	643	11.9
56–118 days	16,267	635.9	13,424	587.3	7.6	(-14.1 to 18.3)	49	(-92 to 120)	1094	42.8	771	31.1
Sensitivity analysis (including the 946,272 matched pairs still at risk on day 7)												
Overall (7–118 days)¹	50,185	1102.2	39,305	938.7	14.8	(3.1 to 20.5)	235	(157 to 350)	3537	79.8	2161	52.0
7–28 days	17,346	214.2	12,865	158.2	26.1	(23.2 to 28.8)	54	(47 to 62)	1220	15.3	689	8.6
28–56 days	15,856	291.1	12,153	223.8	23.1	(20.0 to 26.1)	33	(26 to 40)	1165	21.6	643	11.9
56–118 days	16,267	635.9	13,424	587.3	7.6	(-14.1 to 18.3)	160	(75 to 282)	1094	42.8	771	31.1

RRR, relative risk reduction; RD, risk difference; CI, confidence intervals (based on percentiles derived from non-parametric bootstrapping with 1,000 sampling repetitions).

¹ The analyses by time-interval include only matched pairs still at risk at the start of each of them.

an individual was eligible to receive a 2nd booster dose (i.e., at least 120 days after the administration of the 1st booster dose in Italy), rather than the absolute effectiveness using unvaccinated individuals as reference. Given that almost all the elderly population in Italy had received at least one vaccine dose at the starting date of the study, it is likely that using the very few unvaccinated individuals as the reference group would have introduced a selection bias due to their probably different health and behavioural characteristics. In light of this, it should be considered that the estimates of relative effectiveness presented in this article are likely an underestimate of the absolute effectiveness, given the residual vaccine-induced protection that might persist 120 days or more after the receipt of a 1st booster dose.

Our results are difficult to compare with findings from other studies because of differences in the study population, study design, study period, length of follow-up, outcomes definition, and definition of the unexposed group serving as reference [5–13]. In general, our estimates of relative effectiveness appear lower than those from other studies conducted among the general elderly population [5–13]. This is probably due to the fact that all these studies also included persons aged 60–79 years, who are likely to have a better immune response compared to those aged ≥ 80 years (the population analysed in our study). Moreover, these studies were conducted during predominance of the Omicron BA.1 and BA.2 subvariants [24], while our study also includes an epidemic period with predominant circulation of the Omicron BA.5 subvariant, which has been suggested to reduce the protection induced by the currently available vaccines or prior infection [25]. Also, most of these studies were likely based on a more specific case definition of severe disease compared to our study, possibly leading to higher estimates of relative vaccine effectiveness. Finally, although relative effectiveness of a 2nd booster dose was always estimated as compared to a 1st booster given at least four months earlier, it is possible that the residual vaccine-induced protection in the comparator group differed among studies depending on how the individuals included in this group were distributed over the time span from four months onwards after the 1st booster dose.

This study has some limitations. First, as all observational studies, although we adjusted the analysis for several baseline characteristics through matching, a residual bias due to uncontrolled confounders might remain. For example, a lower propensity to testing and a higher exposure to risky behaviours in individuals who received the 2nd booster vaccine dose, who could feel more protected compared to those who only received the 1st booster vaccine dose by more than 120 days [26], might have biased our estimates towards an overestimation and underestimation, respectively. However, in general, compared to younger age groups, individuals aged ≥ 80 years have contacts with health services more frequently and therefore a higher probability to get advice for testing in case of symptoms [27]. Moreover, they are less likely to be involved in risky social activities and more likely to adopt preventive measures [28,29], thus limiting this potential bias. Second, although no priority access criteria were in place during the study period for the elderly ≥ 80 years, it is likely that those at higher risk of severe COVID-19 had received a 2nd booster dose earlier than those without any risk condition. Thus, it is possible that individuals at higher risk were over-represented in the late follow-up period, possibly leading to overestimate the waning of relative vaccine effectiveness against severe COVID-19, even though our estimates were adjusted for the presence/absence of high-risk conditions and week of administration of the 1st booster dose. Third, SARS-CoV-2 infections self-diagnosed through at-home testing are not reported in the surveillance system and therefore not considered in this analysis. If the utilization of such diagnostics tools did not differ between

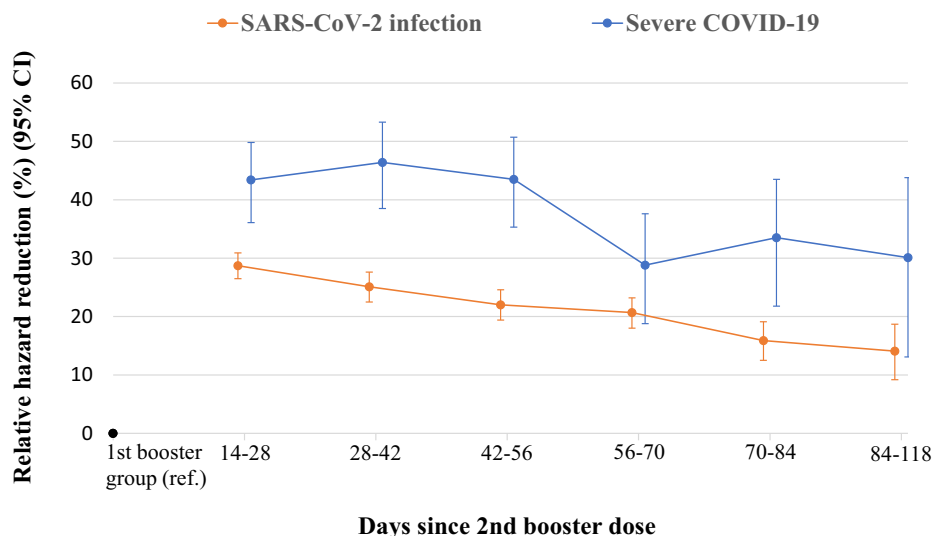


Fig. 4. Relative hazard reduction of SARS-CoV-2 infection and severe COVID-19 at different time intervals after the administration of a second booster vaccine dose (sensitivity analysis).

the two compared groups, our estimates of RRRs are unbiased while RDs are likely underestimated, depending on the proportion of real infections detected through self-testing. However, it is worthwhile to note that part of unreported cases who self-tested positive less than 120 days before the start of the study could have remained included in the unexposed group after matching. This could have led to an underestimation of RRRs, given their likely decision to postpone vaccination with a 2nd booster dose because of the relatively recent naturally-acquired protection. Fourth, although regional health authorities were recommended to report to the national surveillance system only hospitalisations directly attributable to SARS-CoV-2 infection, we cannot exclude that, especially during prevalent circulation of the Omicron BA.5 subvariant, cases hospitalised for other causes and incidentally tested positive for SARS-CoV-2 infection at admission might have been misclassified, possibly leading to an underestimate of the relative effectiveness against severe COVID-19. Finally, our study is based on four months of follow-up after administration of a 2nd booster dose of vaccine and a longer observation period would be necessary to better investigate the waning of vaccine-induced protection, as observed in Italy after completion of the primary vaccination cycle [30].

5. Conclusions

As compared to a 1st booster dose given at least four months earlier, relative vaccine effectiveness against SARS-CoV-2 infection was much reduced 2–4 months after a 2nd booster dose, a time-interval that overlaps with a calendar period where the Omicron BA.5 subvariant was prevalent in Italy. However, on the same time-interval, relative vaccine effectiveness against severe COVID-19 was estimated at about 30%. The cost-benefit of a 3rd booster dose of adapted bivalent COVID-19 vaccine for the elderly people who received the 2nd booster dose at least four months earlier should be carefully evaluated.

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Data sharing

Because of data sharing legal restrictions, the dataset including individual records cannot be made publicly available.

Authors' contribution

MF, AMU, CS, MCR, and PPe designed the study. DP, MB, MDM, AB, and FR retrieved and ensured the quality of COVID-19 surveillance data. VP, SBA, and AS retrieved and ensured the quality of vaccination data. MF, AMU, CS, and PPe carried out the analysis. MF, AMU, CS, MCR, and PPe wrote the manuscript, subsequently reviewed by FMI, PPO, ATP, GR, and SBr. All authors critically revised and approved the submission of the final version of the manuscript.

Data availability

The authors do not have permission to share data.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2022.11.013>.

References

- [1] Patalon T, Saciuk Y, Peretz A, Perez G, Lurie Y, Maor Y, et al. Waning effectiveness of the third dose of the BNT162b2 mRNA COVID-19 vaccine. *Nat Commun* 2022;13:3203.
- [2] Italian Medicines Agency (AIFA). Inserimento dell'indicazione «seconda dose booster» dei medicinali «Comirnaty» e «Spikevax» nell'elenco dei medicinali ai sensi della legge 23 dicembre 1996, n. 648. (Determina n. DG/153/2022). 11 April 2022. https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2022-04-11&atto.codiceRedazionale=22A02405&elenco30giorni=true [accessed 4 September 2022].
- [3] Italian Medicines Agency (AIFA). Modifica della determina n. DG/153/2022 dell'11 aprile 2022 di inserimento dell'indicazione «seconda dose booster» dei medicinali «Comirnaty» e «Spikevax» nell'elenco dei medicinali ai sensi della legge 23 dicembre 1996, n. 648. (Determina n. DG/301/2022). (22A04093) (GU Serie Generale n.161 del 12-07-2022). 12 July 2022. https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2022-07-12&atto.codiceRedazionale=22A04093&elenco30giorni=false [accessed 4 September 2022].
- [4] GitHub. Italia / Covid-19-opendata-vaccini. <https://github.com/italia/covid19-opendata-vaccini/tree/master/dati> [accessed 4 September 2022].
- [5] Grewal R, Kitchen SA, Nguyen L, Buchan SA, Wilson SE, Costa AP, et al. Effectiveness of a fourth dose of Covid-19 mRNA vaccine against the Omicron variant among long term care residents in Ontario, Canada: test negative design study. *BMJ* 2022;378:e071502.
- [6] Muhsen K, Maimon N, Mizrahi AY, Boltyansky B, Bodenheimer O, Diamant ZH, et al. Association of Receipt of the Fourth BNT162b2 Dose With Omicron Infection and COVID-19 Hospitalizations Among Residents of Long-term Care Facilities. *JAMA Intern Med* 2022;182:859–67.
- [7] Magen O, Waxman JG, Makov-Assif M, Vered R, Dicker D, Hernán MA, et al. Fourth Dose of BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. *N Engl J Med* 2022;386:1603–14.
- [8] Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Amir O, Freedman L, et al. Protection by a Fourth Dose of BNT162b2 against Omicron in Israel. *N Engl J Med* 2022;386:1712–20.
- [9] Arbel R, Sergienko R, Friger M, Peretz A, Beckenstein T, Yaron S, et al. Effectiveness of a second BNT162b2 booster vaccine against hospitalization and death from COVID-19 in adults aged over 60 years. *Nat Med* 2022;28:1486–90.
- [10] Gazit S, Saciuk Y, Perez G, Peretz A, Pitzer VE, Patalon T. Short term, relative effectiveness of four doses versus three doses of BNT162b2 vaccine in people aged 60 years and older in Israel: retrospective, test negative, case-control study. *BMJ* 2022;377:e071113.
- [11] Regev-Yochay G, Gonen T, Gilboa M, Mandelboim M, Indenbaum V, Amit S, et al. Efficacy of a Fourth Dose of Covid-19 mRNA Vaccine against Omicron. *N Engl J Med* 2022;386:1377–80.
- [12] Cohen MJ, Oster Y, Moses AE, Spitzer A, Benenson S. Association of Receiving a Fourth Dose of the BNT162b Vaccine With SARS-CoV-2 Infection Among Health Care Workers in Israel. *JAMA Netw Open* 2022;5:e2224657.
- [13] Link-Gelles R, Levy M, Gaglani M, Irving SA, Stockwell M, Dascomb K, et al. Effectiveness of 2, 3, and 4 COVID-19 mRNA Vaccine Doses Among Immunocompetent Adults During Periods when SARS-CoV-2 Omicron BA.1 and BA.2/BA.2.12.1 Sublineages Predominated – VISION Network, 10 States, December 2021–June 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:931–39.
- [14] Italian Government, Presidency of the Council of Ministers. Data repository. <https://www.governo.it/it/dipartimenti/commissario-straordinario-lemergenza-covid-19/15974> [accessed 4 September 2022].
- [15] Italian National Institute of Health, EpiCentro. Epidemiology for public health - COVID-19 integrated surveillance: key national data. <https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-integrated-surveillance-data> [accessed 4 September 2022].
- [16] Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol* 2016;183:758–64.
- [17] Abu-Raddad LJ, Chemaitelly H, Ayoub HH, AlMukdad S, Yassine HM, Al-Khatib HA, et al. Effect of mRNA Vaccine Boosters against SARS-CoV-2 Omicron Infection in Qatar. *N Engl J Med* 2022;386:1804–16.
- [18] Italian National Institute of Health (ISS). Stima della prevalenza delle varianti VOC (Variant Of Concern) e di altre varianti di SARS-CoV-2 in Italia (Indagine del 04/04/2022). 4 April 2022. <https://www.epicentro.iss.it/coronavirus/pdf/sars-cov-2-monitoraggio-varianti-indagini-rapide-4-aprile-2022.pdf> [accessed 4 September 2022].
- [19] Italian National Institute of Health (ISS). Stima della prevalenza delle varianti VOC (Variant Of Concern) e di altre varianti di SARS-CoV-2 in Italia (Indagine del 05/07/2022). 7 July 2022. <https://www.epicentro.iss.it/coronavirus/pdf/sars-cov-2-monitoraggio-varianti-indagini-rapide-5-luglio-2022.pdf> [accessed 4 September 2022].
- [20] Italian National Institute of Statistics (Istat). I.Stat Tavole di mortalità. http://dati.istat.it/Index.aspx?DataSetCode=DCIS_MORTALITA1 [accessed 4 September 2022].
- [21] Italian Ministry of Health. Avvio della somministrazione di dosi “booster” nell'ambito della campagna di vaccinazione anti SARS-CoV-2/COVID-19. 27 September 2021. <https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2021&codLeg=82953&parte=1%20&serie=null> [accessed 4 September 2022].
- [22] European Centre for Disease Prevention and Control (ECDC). Case definition for coronavirus disease 2019 (COVID-19), as of 3 December 2020. <https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition> [accessed 4 September 2022].
- [23] World Health Organization (WHO). International guidelines for certification and classification (coding) of COVID-19 as cause of death. [https://www.who.int/publications/m/item/international-guidelines-for-certification-and-classification-\(coding\)-of-covid-19-as-cause-of-death](https://www.who.int/publications/m/item/international-guidelines-for-certification-and-classification-(coding)-of-covid-19-as-cause-of-death) [accessed 4 September 2022].
- [24] Kliker L, Zuckerman N, Atari N, Barda N, Gilboa M, Nemet, et al. COVID-19 vaccination and BA.1 breakthrough infection induce neutralising antibodies which are less efficient against BA.4 and BA.5 Omicron variants, Israel, March to June 2022. *Euro Surveill* 2022;27:2200559.
- [25] Cao Y, Yisimayi A, Jian F, Son W, Xiao T, Wang L, et al. BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection. *Nature* 2022;608:593–602.
- [26] Falahi S, Mohamadi J, Sayyadi H, Pakzad I, Rashidi A, Naserifar R, et al. COVID-19 vaccination, Peltzman Effect and possible increase in high-risk behaviors: a growing concern on risk compensation and reduced compliance to Public Health protective Measures after vaccines rollout. *Infect Disord Drug Target* 2022; doi: 10.2174/1871526522666220419133849 (online ahead of print).
- [27] Graham MS, May A, Varsavsky T, Sudre CH, Murray B, Kläser K, et al. Knowledge barriers in a national symptomatic-COVID-19 testing programme. *PLOS Glob Public Health* 2021;2:e0000028.
- [28] Kim JK, Crimmins EM. How does age affect personal and social reactions to COVID-19: Results from the national Understanding America Study. *PLoS ONE* 2020;15:e0241950.
- [29] Korn L, Siegers R, Eitze S, Sprengel P, Taubert F, Böhm R, et al. Age Differences in COVID-19 Preventive Behavior. *Eur Psychol* 2021;26:359–72.
- [30] Fabiani M, Puopolo M, Morciano C, Spuri M, Spila Alegiani S, Filia A, et al. Effectiveness of mRNA vaccines and waning of protection against SARS-CoV-2 infection and severe covid-19 during predominant circulation of the delta variant in Italy: retrospective cohort study. *BMJ* 2022;376:e069052.