Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Effectiveness against severe COVID-19 of a seasonal booster dose of bivalent (original/Omicron BA.4-5) mRNA vaccines in persons aged ≥60 years: Estimates over calendar time and by time since administration during prevalent circulation of different Omicron subvariants, Italy, 2022–2023

Massimo Fabiani [a,*], Alberto Mateo-Urdiales [a], Chiara Sacco [a,b], Emmanouil Alexandros Fotakis [a,b], Serena Battilomo [c], Daniele Petrone [a], Martina Del Manso [a], Antonino Bella [a], Flavia Riccardo [a], Paola Stefanelli [a], Anna Teresa Palamara [a], Patrizio Pezzotti [a], on behalf of the Italian Integrated Surveillance of COVID-19 study group and of the Italian COVID-19 Vaccines Registry group

[a] Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Viale Regina Elena 299, 00161 Rome, Italy
[b] European Programme on Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control, Stockholm, Sweden
[c] General Directorate of Health Information System and Statistics, Italian Ministry of Health, Viale Giorgio Ribotta 5, 00144 Rome, Italy

ARTICLE INFO

Keywords:
SARS-CoV-2
Omicron subvariants
COVID-19
Bivalent mRNA vaccines
Effectiveness
Elderly population

ABSTRACT

Evaluating how a COVID-19 seasonal vaccination program performed might help to plan future campaigns. This study aims to estimate the relative effectiveness (rVE) against severe COVID-19 of a seasonal booster dose over calendar time and by time since administration.

We conducted a retrospective cohort analysis among 13,083,855 persons aged ≥60 years who were eligible to receive a seasonal booster at the start of the 2022–2023 vaccination campaign in Italy. We estimated rVE against severe COVID-19 (hospitalization or death) of a seasonal booster dose of bivalent (original/Omicron BA.4-5) mRNA vaccines by two-month calendar interval and at different times post-administration. We used multivariable Cox regression models, including vaccination as time-dependent exposure, to estimate adjusted hazard ratios (HR) and rVEs as [(1-HR)X100].

The rVE of a seasonal booster decreased from 64.9% (95% CI: 59.8–69.4) in October-November 2022 to 22.0% (95% CI: 15.4–28.0) in April-May 2023, when the majority of vaccinated persons (67%) had received the booster at least 4–6 months earlier. During the epidemic phase with prevalent circulation of the Omicron BA.5 subvariant, rVE of a seasonal booster received ≤90 days earlier was 83.0% (95% CI: 79.1–86.1), compared to 37.4% (95% CI: 25.5–47.5) during prevalent circulation of the Omicron XBB subvariant. During the XBB epidemic phase, rVE was estimated at 15.8% (95% CI: 9.1–20.1) 181–369 days post-administration of the booster dose. In all the analyses we observed similar trends of rVE between persons aged 60–79 and those ≥80 years, although estimates were somewhat lower for the oldest group.

A seasonal booster dose received during the vaccination campaign provided additional protection against severe COVID-19 up to April-May 2023, after which the incidence of severe COVID-19 was much reduced. The results also suggest that the Omicron XBB subvariant might have partly escaped the immunity provided by the seasonal booster targeting the original and Omicron BA.4-5 strains of SARS-CoV-2.

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; EMA, European Medicines Agency; RVE, relative vaccine effectiveness; PCR, polymerase chain reaction; SED, socioeconomic deprivation; ECDC, European Centre for Disease Prevention and Control; WHO, World Health Organization; IQR, interquartile range; HR, hazard ratio; CI, confidence interval.

* Corresponding author.
E-mail address: massimo.fabiani@iss.it (M. Fabiani).

https://doi.org/10.1016/j.vaccine.2024.05.074
Received 28 February 2024; Received in revised form 21 May 2024; Accepted 31 May 2024

1. Introduction

Since its first introduction in late 2020, vaccination has been the main mitigation tool used to face the coronavirus disease 2019 (COVID-19). By the end of 2023, about two-thirds of the worldwide population had received a primary vaccination cycle, and one-third had also received an additional booster dose [1]. However, the infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still causing high morbidity and mortality, with almost 70 million cases of SARS-CoV-2 infection and 320,000 COVID-19 related deaths reported worldwide in 2023 [1]. The protective effect of COVID-19 vaccines has been observed in both experimental [2–6] and observational studies [7–9]. However, waning of vaccine-induced immunity over time since administration [10,11] and the diffusion of new SARS-CoV-2 variants, possibly more transmissible and able to evade the acquired immunity [12,13], indicate that additional seasonal booster doses with vaccines adapted to the circulating SARS-CoV-2 sub-lineages are required to maintain high levels of protection against infection and severe COVID-19. To this purpose, in the early autumn 2022, the European Medicines Agency (EMA) approved the utilisation of the adapted bivalent mRNA vaccines manufactured by Pfizer/BioNtech and Moderna targeting the original and Omicron BA.4-5 subvariants [14,15].

Following the EMA's indications, in view of the 2022–2023 autumn/winter vaccination campaign, the Italian health authorities recommended a booster dose of bivalent mRNA vaccines to all persons $\geq$ 60 years of age and other high-risk population groups who had the primary vaccination cycle completed and no prior infections or additional booster doses in the last 120 days [16]. As of January 2022, person aged 60 years and above residing in Italy, the main target of the vaccination campaign, were about 18,1 million (31% of the total residing population) [17]. Of these, about 13,4 million (74%) were eligible to receive a seasonal booster dose of vaccine by late September 2022 [18].

In this study, conducted among persons $\geq$ 60 years of age who were eligible to receive a seasonal booster dose at the start of the 2022–2023 vaccination campaign, we aimed to estimate the relative effectiveness (rVE) against severe COVID-19 of a seasonal booster dose of bivalent (original/Omicron BA.4-5) mRNA vaccines over calendar time after the start of the campaign and by time since administration during prevalent circulation of different Omicron subvariants. We also aimed to measure the impact of the vaccination campaign with bivalent (original/Omicron BA.4-5) mRNA vaccines through estimating the number of averted severe COVID-19 cases.

2. Methods

2.1. Data sources

We used data extracted on 5 January 2024 from the National Vaccination registry (held by the Ministry of Health) and from the National COVID-19 Integrated Surveillance System (coordinated by the Italian National Institute of Health) [19,20]. We conducted a deterministic record linkage using the individual tax code as a key variable to merge these datasets. The National Vaccination registry includes information on dates and vaccine brands for all vaccine administrations, together with demographic and clinical characteristics of all people who received at least one dose of a COVID-19 vaccine. The National COVID-19 Surveillance System records data on all cases of SARS-CoV-2 infection who were laboratory-confirmed through polymerase chain reaction (PCR) or antigen tests in medically attended facilities (pharmacies and private/public health centres). It includes information on the date of positive testing and clinical outcomes (e.g., COVID-19 related hospitalization and death). No information on possible deaths occurring for causes unrelated to COVID-19 was available from these data sources. Therefore, we used the publicly available life tables by region, age, and sex for the year 2019 (when SARS-COV-2 was not circulating in Italy) to impute the expected date of death for causes other than COVID-19 [21] (Supplementary Methods S1 for more details). Moreover, we also used the last available information on the levels of urbanization and socio-economic deprivation (SED) of the Italian municipalities, which was linked to individual records through the municipality's code where vaccination took place [22,23]. Finally, we used data retrieved from the TESSy database, managed by the European Centre for Disease Prevention and Control (ECDC), to identify the epidemic phases characterised by the prevalent circulation of different SARS-CoV-2 Omicron subvariants [24].

2.2. Study design and selection of participants

Based on this data, we conducted a nationwide retrospective cohort analysis among persons $\geq$ 60 years of age who were eligible to receive the seasonal vaccine at the starting date of the campaign on 26 September 2022 (i.e., those with at least the primary vaccination cycle completed and no laboratory-confirmed prior infections or additional booster doses in the last 120 days). For different observation periods between 26 September 2022 and 30 September 2023 (i.e.,two-month calendar intervals as of the start of the campaign and periods with prevalent circulation of different Omicron subvariants), we compared time to laboratory-confirmed SARS-CoV-2 infection leading to severe COVID-19 (i.e., hospitalization or death occurring within 28 days since testing positive) between persons who received a booster dose with bivalent (original/Omicron BA.4-5) mRNA vaccines during the seasonal vaccination campaign (26 September 2022 to 31 March 2023) and those who did not. According to Italian guidelines, based on indications from the World Health Organization (WHO) [25], a COVID-19 related death was defined as that occurred in presence of a clinical picture suggestive of COVID-19, the absence of a clear cause of death different from COVID-19 (e.g., trauma), and the absence of a complete clinical recovery from the disease. Likewise, only the hospitalisations of cases with clinical manifestations of the respiratory tract or other organs directly associated to SARS-CoV-2 infection are expected to be reported to the surveillance system.

After the initial selection of the eligible population $\geq$ 60 years of age, we excluded persons with missing information for vaccination (i.e., vaccination date or vaccine brand), dates of hospitalization or death, or other variables considered in the analysis. We also excluded persons with inconsistent data and those who received a booster dose other than the bivalent (original/Omicron BA.4-5) mRNA vaccine on the starting date of the vaccination campaign) (Fig. 1).

2.3. Statistical analysis

We conducted a time-to-event analysis, with individual follow-up starting at the beginning of the vaccination campaign on 26 September 2022 and ending on the first of the following dates: the date of laboratory-confirmed infection subsequently leading to severe COVID-19, the imputed date of death for causes unrelated to COVID-19, the date of administration of a seasonal booster with vaccines other than the bivalent (original/Omicron BA.4-5) mRNA ones, the date of vaccine administration after the end of the seasonal campaign (31 March 2023), the date of a second booster dose received during the study period, or the end of the study period on 30 September 2023.

After splitting individual data to account for time-varying vaccination status, we performed a multivariable Cox proportional hazards regression analysis, using calendar time measured in days as the underlying time scale, to estimate the adjusted hazard ratio (HR) of severe COVID-19 in the eligible persons who received a seasonal booster dose compared to those who did not. A Cox proportional hazard model was run separately for each two-month calendar period (October November 2022 to August-September 2023).

Moreover, the same model was used to estimate HRs according to time since administration of the seasonal booster (i.e., 15–90 days, 91–180 days, and $>$ 180 days) during three different epidemic phases

characterised by the prevalent circulation of the Omicron subvariants BA.5 (weeks 39–46/2022; 74.3%), BQ.1 (week 47/2022–8/2023; 56.2%) and XBB (week 9–39/2023; 86.8%) (Fig. 2) [24]. In this model, including the interaction between vaccination status and epidemic phase, we excluded persons who had received a diagnosis of SARS-CoV-2 infection between the starting date of the vaccination campaign and the starting date of the respective epidemic phase.

All the analyses were stratified by age group (i.e., 65–79 years and ≥ 80 years) and estimates were adjusted for sex, age (5-year age groups from 60 to 64 up to 90–94 and then grouping ≥ 95 years), country of birth (born in Italy or abroad), geographical area where the last vaccination took place (19 regions and two autonomous provinces of Italy), high-risk conditions (none, residence in long term care facilities, immunocompromisation, other health-risk conditions; Supplementary Table S1 for more details), number of doses received before the starting date of the study (2, 3, or 4), and urbanization level (high, medium, low) and SED level (1st quintile-least deprived to 5th quintile-most deprived) of the municipality of where vaccination took place. The rVE estimates were calculated as [(1-HR) X 100] and presented together with their 95% confidence intervals (CI).

Finally, we conducted an analysis where, using a formula based on rVE, vaccine uptake and number of observed events by two-month calendar period and age group, we estimated the number of severe COVID-19 cases averted through the vaccination campaign with bivalent (original/Omicron BA.4-5) mRNA vaccines [26,27]. We also estimated the expected number of averted cases according to scenarios where vaccine uptake during the seasonal campaign was set at different levels (i.e., 50%, 75% and 90%).

2.4. Ethics

This study, based on routinely collected data, was not submitted for

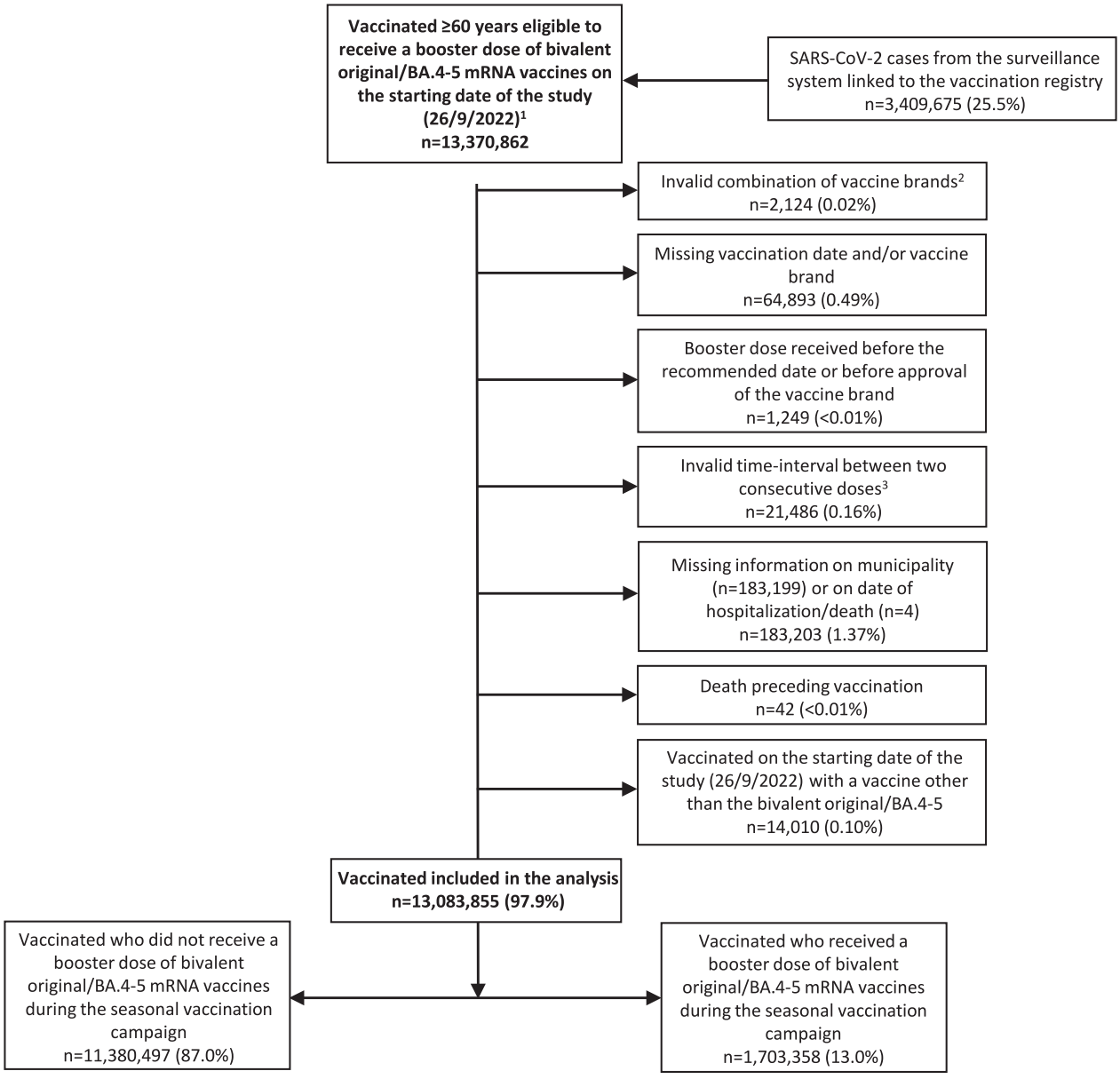

Fig. 1. Selection of study participants eligible to receive a booster dose of bivalent (original/Omicron BA.4-5) mRNA vaccines at the start of the seasonal vaccination campaign (Italy, 26 September 2022 – 31 March 2023). [1] Persons with completed primary vaccination cycle who received the last vaccine dose and had a possible prior SARS-CoV-2 infection more than 120 days before the start of the vaccination campaign. [2] Combination of vaccines not foreseen by the national recommendations (e.g., first booster with non-mRNA vaccines) [3] Less than 19 days between the first and second dose, and less than 90 days between the second and third dose or between two consecutive booster doses.

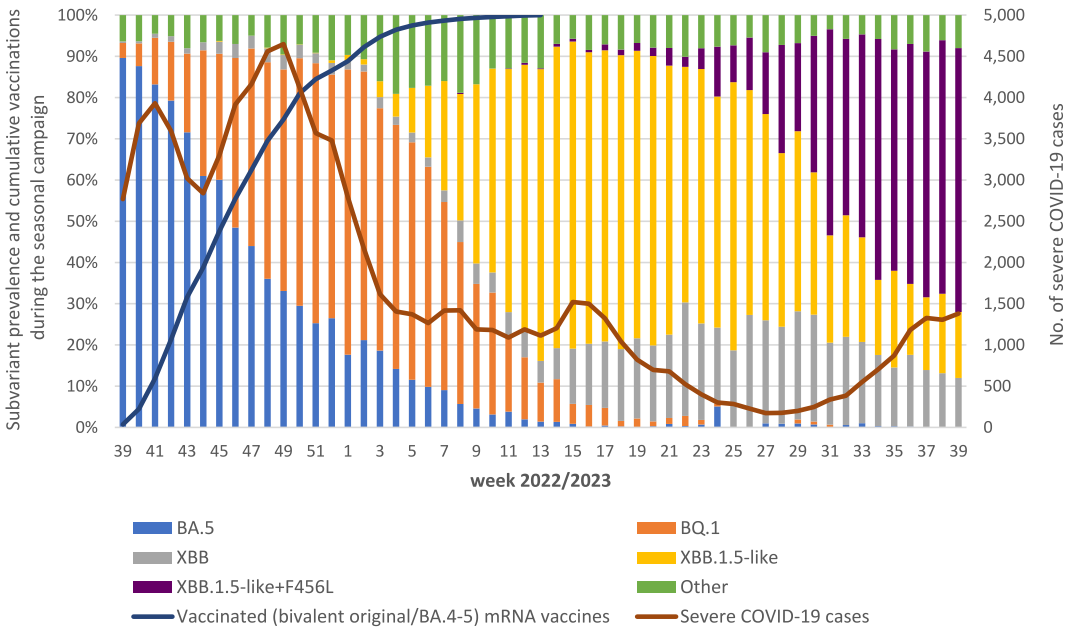

Fig. 2. Prevalence of circulating Omicron SARS-CoV-2 subvariants, cumulative vaccinations during the seasonal campaign, and number of severe COVID-19 cases by calendar week (Italy, 26 September 2022 – 30 September 2023).

approval to an ethical committee because the dissemination of COVID-19 surveillance data was authorized by Law number 52 on 19 May 2022 (article 13). Because of the retrospective design and the large size of the population under study, in accordance 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

Of the 13,370,862 persons ≥ 60 years eligible to receive a booster dose of bivalent (original/Omicron BA.4-5) mRNA vaccines on the starting date of the study, we excluded 287,007 (2.1%) persons with missing information or inconsistent data for vaccination, clinical outcome or other variables considered in the study (Fig. 1). We therefore included 13,083,855 persons in the analysis, 1,703,358 (13.0%) of whom received a seasonal booster dose of bivalent (original/Omicron BA.4-5) mRNA vaccines during the vaccination campaign, most of them on or before 31 December 2022 (n = 1,474,251; 86.5%). Almost all the persons who received a seasonal booster dose of these vaccines were vaccinated with the Comirnaty bivalent (original/Omicron BA.4-5) mRNA vaccine manufactured by Pfizer/BioNTech (n = 1,669,910; 98.0%), while the remaining received the Spikevax bivalent (original/Omicron BA.4-5) mRNA vaccine manufactured by Moderna (n = 33,448; 2.0%). Of the 13,083,855 persons included in the analysis, 780,529 (6.0%) had received a seasonal booster dose of other COVID-19 vaccines, mostly the bivalent (original/Omicron BA.1) mRNA vaccines (97%), and were censored at the date of receipt of the seasonal booster in the time-to-event analysis.

3.1. Demographic and clinical characteristics of the study population

The demographic and clinical characteristics of vaccinated persons included in the study are presented in Table 1.

We did not observe substantial differences in the distribution by sex between individuals who received the seasonal booster and those who did not, while we observed a higher median age in the former group (74 years; IQR: 67–81 vs. 71 years; IQR: 65–79). Among persons who did not receive the seasonal booster dose, we observed a relatively higher proportion of foreign-born individual (4.8% vs. 3.0%), residents in southern Italy (37.7% vs. 20.1%), and residents in most deprived municipalities (52.6% vs. 39.6%). Those who received the seasonal booster had more frequently received a prior booster dose (96.1% vs 85.8%) and were more frequently presenting high-risk conditions (71.1% vs. 56.5%) and living in urban municipalities (39.8% vs. 33.5%).

3.2. Relative vaccine effectiveness against severe COVID-19 over calendar time

Among the 13,083,855 persons included in the analysis, we observed 51,176 (0.39%) cases of severe COVID-19; 3,759 (0.22%) in those who received the seasonal booster and 47,417 (0.42%) in those who did not.

The rVE against severe COVID-19 of a seasonal booster dose of bivalent (original/Omicron BA.4-5) mRNA vaccines peaked during the first two months of the vaccination campaign (October-November 2022), when it was estimated at 68.3% (95% CI: 60.7–74.4) in persons aged 60–79 years and 62.6% (95% CI: 55.4–68.6) in those aged 80 years and above (Fig. 3-A; Supplementary Table S2). It then decreased over the following two-month calendar intervals, from December-January 2023, at the end of which 96.8% of persons vaccinated with the seasonal booster during the campaign had already received it (Fig. 2), to April-May 2023, when the seasonal booster was still showing a significant protective effect (rVE = 25.3%; 95% CI: 15.4–34.1 in the 60–79 years age group and rVE = 19.5%; 95% CI: 10.5–27.6 in the ≥ 80 years age group). During the summer period, from June to September 2023, we did not observe any significant protection conferred by a seasonal booster dose administered during the vaccination campaign which ended on 31 March 2023.

3.3. Relative vaccine effectiveness against severe COVID-19 over time since booster dose

In the period when the Omicron BA.5 subvariant was prevalent in Italy (weeks 39–46/2022; 74.3%) (Fig. 2), the rVE against severe COVID-19 of a seasonal booster received ≤ 90 days earlier was 86.3% (95% CI: 80.8–90.3) in the 60–79 years age group and 80.4% (95% CI: 74.8–84.8) in the ≥ 80 years age group (Fig. 3-B). The rVE in the same time interval since the booster dose was lower in the calendar period

Table 1
Baseline characteristics of the individuals included in the analysis (Italy, 26 September 2022).

	Did not receive seasonal booster[1] n = 11,380,497		Received seasonal booster[1] n = 1,703,358		Total n = 13,083,855	
	n	%	n	%	n	%
Sex						
Female	6,249,507	54.9	906,528	53.2	7,156,035	54.7
Male	5,130,990	45.1	796,830	46.8	5,927,820	45.3
Age						
60–64 years	2,753,230	24.2	259,368	15.2	3,012,598	23.0
65–69 years	2,224,237	19.5	306,885	18.0	2,531,122	19.3
70–74 years	1,977,272	17.4	338,088	19.8	2,315,360	17.7
75–79 years	1,586,242	13.9	298,120	17.5	1,884,362	14.4
80–84 years	1,377,089	12.1	256,165	15.0	1,633,254	12.5
85–89 years	897,573	7.9	157,400	9.2	1,054,973	8.1
90–94 years	431,907	3.8	69,730	4.1	501,637	3.8
≥95 years	132,947	1.2	17,602	1.0	150,549	1.2
Median (IQR)	71 (65–79)		74 (67–81)		72 (65–80)	
Country of birth						
Italian-born	10,837,461	95.2	1,652,151	97.0	12,489,612	95.5
Foreign-born	543,036	4.8	51,207	3.0	594,243	4.5
Geographical macroarea						
North-West	2,943,731	25.9	595,282	34.9	3,539,013	27.0
North-East	2,106,764	18.5	324,321	19.0	2,431,085	18.6
Centre	2,255,422	19.8	429,238	25.2	2,684,660	20.5
South and Islands	4,074,580	35.8	354,517	20.8	4,429,097	33.9
High-risk group						
None	8,087,966	71.1	962,098	56.5	9,050,064	69.2
LTCF residents	187,775	1.6	31,521	1.9	219,296	1.7
Immunocompromisation[2]	58,633	0.5	15,010	0.9	73,643	0.6
Other health-risk conditions[2]	3,046,123	26.8	694,729	40.8	3,740,852	28.6
Number of prior doses						
2 doses (primary vaccination) doses)	1,613,897	14.2	66,640	3.9	1,680,537	12.8
3 doses (first booster)	9,070,797	79.7	1,468,751	86.2	10,539,548	80.6
4 doses (second booster)	695,803	6.1	167,967	9.9	863,770	6.6
Urbanization level[3]						
High	3,847,802	33.8	689,228	40.5	4,537,030	34.7
Medium	5,404,365	47.5	774,496	45.5	6,178,861	47.2
Low	2,128,330	18.7	239,634	14.1	2,367,964	18.1
Deprivation level[3]						
1st quintile (least deprived)	932,504	8.2	197,192	11.6	1,129,696	8.6
2nd quintile	1,632,430	14.3	300,150	17.6	1,932,580	14.8
3rd quintile	2,831,043	24.9	530,001	31.1	3,361,044	25.7
4th quintile	3,286,621	28.9	453,937	26.6	3,740,558	28.6
5th quintile (most deprived)	2,697,899	23.7	222,078	13.0	2,919,977	22.3

IQR, interquartile range.
[1] Vaccinations status: having received or not a booster dose of mRNA bivalent (original/Omicron BA.4-5) vaccines during the seasonal vaccination campaign (26 September 2022 to 31 March 2023).
[2] Immunocompromisation and other health-risk conditions are listed in Supplementary Table S1.
[3] Urbanization and deprivation levels were based on the municipality where vaccination took place.

when the Omicron BQ.1 subvariant was prevalent (weeks 47/2022–8/2023; 56.2%) (rVE = 58.9%; 95% CI: 55.1–62.4 in the 60–79 years age group and rVE = 56.7%; 95% CI: 53.5–59.7 in the ≥ 80 years age group) and in that with prevalent circulation of the Omicron XBB subvariants (weeks 9–39/2023; 86.8%) (rVE = 39.9%; 95% CI: 20.2–54.8 in the 60–79 years age group and rVE = 35.2%; 95% CI: 19.1–48.2 in the ≥ 80 years age group).

During the Omicron BQ.1 prevalent period, 91–180 days after the seasonal booster dose receipt, the rVE against severe COVID-19 decreased to 45.4% (95% CI: 33.3–55.2) in the 60–79 years age group and to 29.6% (95% CI: 16.6–40.5) in the ≥ 80 years age group. During the period with prevalent circulation of the Omicron XBB subvariants, the rVE decreased to 31.6% (95% CI: 23.6–38.7) 91–180 days after the seasonal booster dose administration and to 20.9% (95% CI: 12.6–28.4) > 180 days later in persons aged 60–79 years. In the same epidemic period, among persons ≥ 80 years of age, the rVE decreased to 22.6% (95% CI: 15.3–29.3) 91–180 days after the seasonal booster dose administration and to 10.3% (95% CI: 2.4–17.6) > 180 days later.

3.4. Number of averted severe COVID-19 cases

Overall, it was estimated that the seasonal vaccination campaign based on a booster dose of bivalent (original/Omicron BA.5–5) vaccines averted 2,320 cases of severe COVID-19 during the study period (4.3% of the expected cases without a vaccination campaign); 975 (4.4%) cases in persons aged 60–79 years and 1,345 (4.3%) in those aged ≥ 80 years (Fig. 4; Supplementary Table S2). We also estimated that, according to scenarios where vaccine uptake during the seasonal campaign was set at 75% and 90%, the total number of averted severe COVID-19 cases would have been 12,650 (23.7%) and 15,178 (28.4%), respectively.

4. Discussion

We found that, in Italy, among people ≥ 60 years of age who received a seasonal booster dose of bivalent (original/Omicron BA.4-5) mRNA vaccines, it conferred additional protection against severe COVID-19 up to April-May 2023, when most of the vaccinated persons included in the analysis (67.4%) had received the seasonal booster at least 4–6 months earlier. We also found that, overall, the autumn/winter vaccination campaign, based on a booster dose of bivalent (original/Omicron

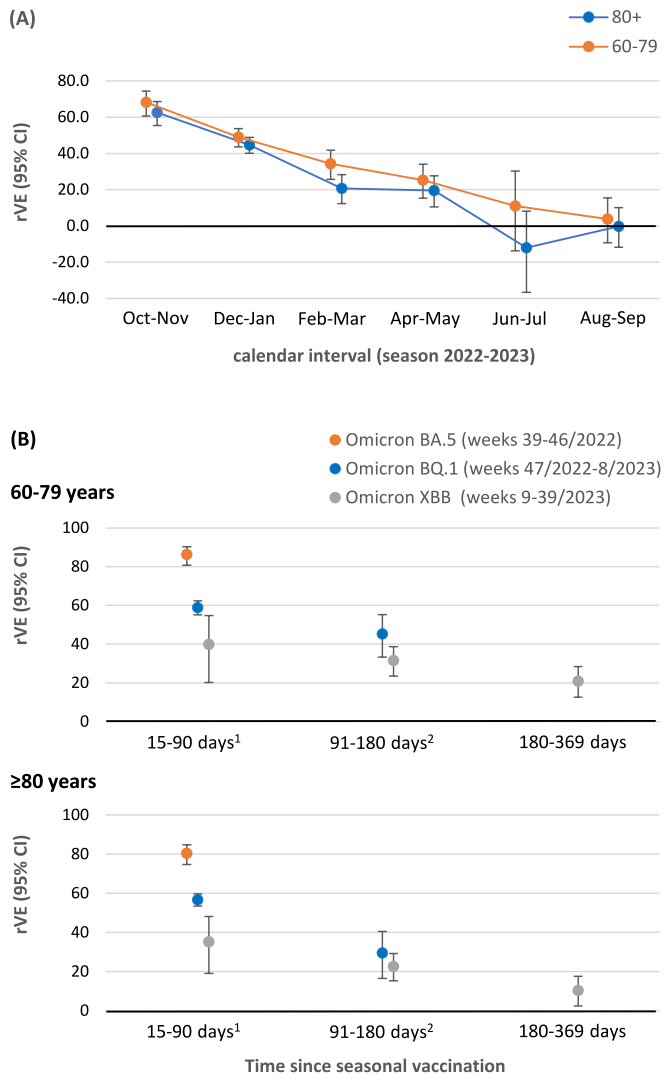

Fig. 3. Age-specific rVE against severe COVID-19 over two-month calendar periods (A) and by time since the seasonal booster administration in different epidemic phases (B) (Italy, 26 September 2022 – 30 September 2023). rVE, relative vaccine effectiveness, CI, confidence interval. [1] The interval post vaccination was 15–55 days for the analysis of the period with prevalent circulation of the Omicron BA.5 variant. [2] The interval post vaccination was 91–153 days for the analysis of the period with prevalent circulation of the Omicron BQ.1 variant.

BA.5–5) vaccines prevented 2,320 cases of severe COVID-19 over 12 months (October 2022 to September 2023), reflecting the low vaccine uptake during the campaign (13%) rather than a low rVE. Most of these cases (93%) were averted during the autumn/winter season (October 2022 to March 2023), when the concomitant circulation of other respiratory viruses and the higher incidence of season-related diseases put healthcare services under pressure. Considering that, according to simulated scenarios, the number of averted cases would have been much higher if vaccine uptake was 75% or more, we think that a seasonal booster dose might have also provided indirect benefits making available additional resources for healthcare services.

In April 2023, the ECDC suggested that a spring 2023 COVID-19 vaccination campaign, targeting the elderly population ≥ 80 years of age and other high-risk groups, could have increased individual protection and have had a substantial effect at population level under specific circumstances, such as high vaccine uptake in both the autumn and spring campaigns [28]. However, in Italy, as mentioned above, vaccine uptake during the 2022–2023 autumn/winter campaign was quite low (19% also considering those who received a booster dose of vaccines different from the bivalent (original/Omicron BA.4-5) mRNA vaccines). Moreover, although in general a predictable pattern of COVID-19 seasonality has not yet been established, the trend of severe COVID-19 cases shown in Fig. 2 indicates that during 2022–2023 the impact of the disease has been higher during the period corresponding to the traditional influenza season, with relatively few cases during the summer months, when we observed no significant residual protection provided by the seasonal booster. All this suggests that, in Italy, a possible spring 2023 vaccination campaign would have not added substantial benefits and the needed resources to implement it were better addressed to other public health priorities. However, it is worthwhile to note that, given the possible emergence of new SARS-CoV-2 variants, the availability of new adapted COVID-19 vaccines, and possible changes in epidemiological trends over time, the expected benefits of a spring vaccination campaign should be re-evaluated year by year.

During 2022–2023, different sublineages of the Omicron SARS-CoV-2 variant were circulating in Italy (Fig. 2). We found that early rVE against severe COVID-19 (15–90 days post-administration) was higher during prevalent circulation of the Omicron BA.5 subvariant compared to periods when the BQ.1 and XBB subvariants were prevalent. Although a comparison of the bivalent (original/Omicron BA.4-5) mRNA vaccines' performance during different epidemic phases may suffer from a bias due to differences in unmeasured characteristics of persons who received the seasonal booster at different times [29], this result suggests that the Omicron BQ.1 and XBB sublineages might have partly escaped the immunity provided by the seasonal booster targeting the original and Omicron BA.4-5 strains of SARS-CoV-2. This is consistent with findings from other studies that showed a relatively low neutralization activity against Omicron BQ.1, and XBB from mRNA bivalent booster [30,31].

Although showing a similar pattern of decrease over six months post-administration, the rVE of a booster dose of bivalent (original/Omicron BA.4-5) mRNA vaccines against severe COVID-19 likely caused by the BQ.1 subvariant was higher compared to that against the severe disease likely due to the Omicron XBB subvariants. We observed a negligible vaccine-induced protection six months after the booster dose administration in persons ≥ 80 years of age during the period when the Omicron XBB subvariants were prevalent. Similar waning of protection against severe COVID-19 likely due to Omicron XBB subvariants was observed in other European countries [32,33].

In all analyses we found rVE estimates slightly lower in persons ≥ 80 years of age compared to those aged 60–79 years, possibly because of a reduced humoral immune response associated with increasing age [34].

This nationwide study, representative of all residents in Italy ≥ 60 years of age, evaluated both the rVE over calendar time, reflecting the timing of vaccine uptake and the epidemic trend during 2022–2023, and the rVE by time since seasonal booster administration.

It has, however, some limitations. First, the analysis was adjusted for several variables but, as for other observational studies, we were not able to control for unmeasured potential confounders that could have affected our estimates (e.g., behavioural factors associated with both vaccine uptake and risk of SARS-CoV-2 infection).

Second, given the high diffusion of self-diagnosis through at-home testing and the possible under-ascertainment of asymptomatic and mild cases, it is likely that many SARS-CoV-2 infections were not reported to the national surveillance system, thus leading to a possible overestimation of the eligible individuals at the start of the vaccination campaign and of each epidemic phase considered in the analysis. This was likely more frequent in those who did not receive the seasonal booster or received it later during the campaign, possibly causing an underestimation of rVE in the first months after the start of the vaccination campaign and after the administration of the seasonal booster dose.

Third, as mentioned before, the comparison of rVE by time since booster administration among different epidemic phases should be

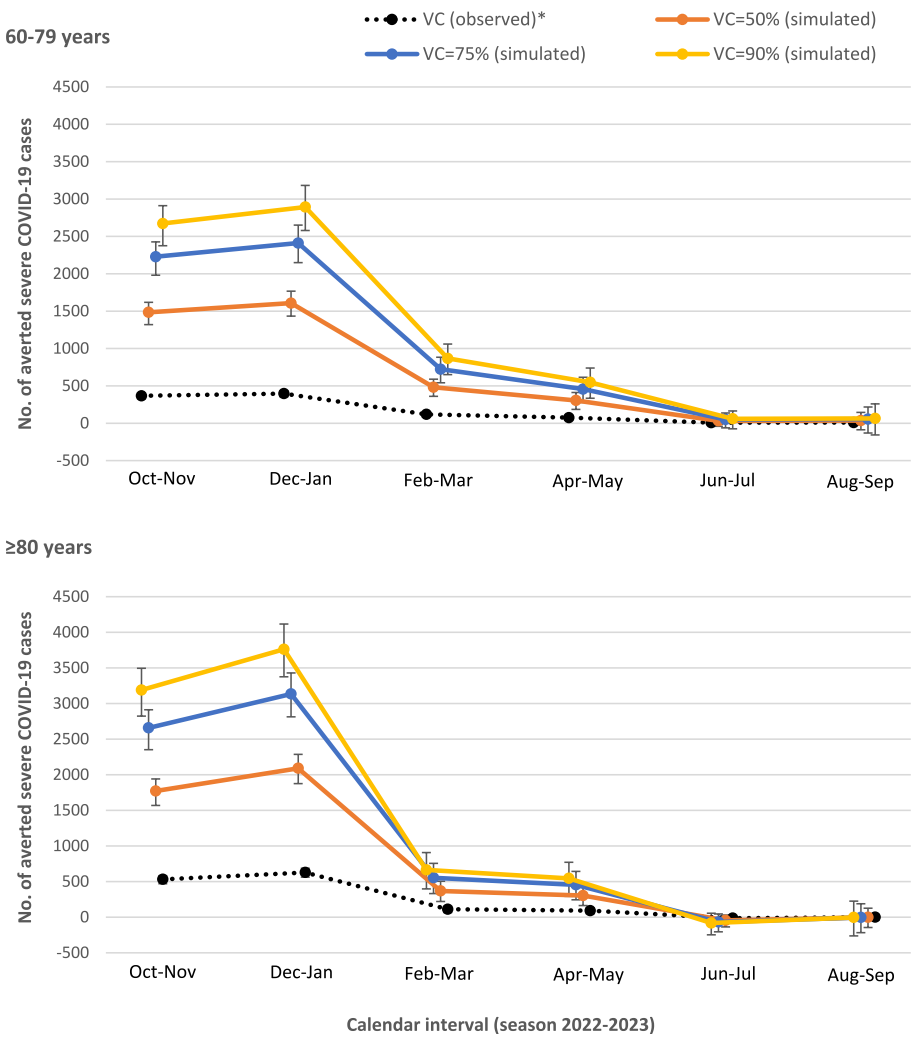

Fig. 4. Number of severe COVID-19 cases averted through the seasonal vaccination campaign and according to scenarios with vaccine uptake set at different levels. VC, vaccination coverage. * VC during the vaccination campaign was 12.3% in persons aged 65–79 years and 15.0% in those ≥80 years of age.

interpreted with cautions because of the possible different unmeasured characteristics among persons who received the seasonal booster at different times [29]. For example, those who received the booster dose later might be generally less prone to adopt preventive measures and therefore have had a higher exposure to risky behaviours than those who received it earlier. This could have resulted in a relative underestimation of rVE during the Omicron XBB epidemic phase, especially early after the seasonal booster, and a slight overestimation of rVE in the previous epidemic phases, especially during the prevalent circulation of the Omicron BA.5 subvariant, when they have contributed to the analysis as unvaccinated with the seasonal booster. Moreover, it should be noted that rVE early after administration of a seasonal booster dose during the Omicron BA.5 epidemic phase was estimated up to 55 days post-administration, as compared to 90 days post-administration during the Omicron BQ.1 and XBB epidemic phases, possibly yielding an overestimation of differences with estimates for the Omicron BQ.1 and XBB prevalence periods. To a lesser extent, this also applies to the comparison of rVE 91–180 days after administration of a seasonal booster dose between the Omicron BQ.1 and XBB epidemic phases, having been possible to estimate the former only up to 153 days post-administration. However, in both cases, censoring the observations at 55 days and 153 days post-administration, respectively, we found increased but still lower rVE estimates 15–55 days post-administration during the BQ.1 and XBB epidemic phases compared to the estimate for the BA5 epidemic phase, as well a negligible increase of the rVE estimate 91–153 days post-administration during the XBB epidemic phase.

Fourth, although the Italian surveillance system foresees only the notification of hospitalisations caused by COVID-19, it is possible that cases incidentally tested positive at admission were misclassified as severe cases, possibly introducing a bias toward underestimation of rVE [35].

Fifth, we adjusted our estimates for the level of socioeconomic deprivation measured at municipality level, which does not necessarily reflect the individual socioeconomic status, especially in large municipalities where heterogeneity between subareas is likely present.

Finally, the study was conducted assuming that all cases included in the analysis for each epidemic phase were due to the Omicron subvariants estimated to be prevalent in that period (Fig. 2). However, a proportion of these cases, especially during the Omicron BQ.1 phase, could have been caused by other co-circulating subvariants, possibly introducing a bias in our estimates.

5. Conclusions

The results of this study suggest that, among persons aged ≥ 60, a booster dose of bivalent (original/Omicron BA.4-5) mRNA vaccines received during the seasonal vaccination campaign conducted in Italy provided additional protection against severe COVID-19 up to April-May 2023, after which the weekly number of severe COVID-19 cases became relatively low. We also found that early rVE against severe COVID-19

(15–90 days post-administration) was higher during prevalent circulation of the Omicron BA.5 subvariant than during the epidemic phases with prevalent circulation of the Omicron BQ.1 and XBB subvariants, suggesting that the latter might have partly escaped the immunity provided by the seasonal booster targeting the original and Omicron BA.4-5 strains of SARS-CoV-2. Further analyses focusing on the currently ongoing 2023–2024 vaccination campaign and those possibly implemented in the following seasons would help in planning the timing and to evaluate the need of adapted booster vaccines according to updated epidemiological data.

Data sharing

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

Authors' contribution

MF, AMU, CS, and PP designed the study. DP, MDM, and AB retrieved and ensured the quality of COVID-19 surveillance data. SB retrieved and ensured the quality of vaccination data. MF, AMU, CS, and PP carried out the analysis. MF, AMU, EAF, and PP wrote the manuscript, subsequently reviewed by FR, PS, and ATP. All authors critically revised and approved the submission of the final version of the manuscript.

Disclaimer

The authors Chiara Sacco and Emmanouil Alexandros Fotakis are fellows of the ECDC Fellowship Programme, supported financially by the European Centre for Disease Prevention and Control. The views and opinions expressed herein do not state or reflect those of ECDC. ECDC is not responsible for the data and information collation and analysis and cannot be held liable for conclusions or opinions drawn.

CRediT authorship contribution statement

Massimo Fabiani: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Alberto Mateo-Urdiales:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Chiara Sacco:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Emmanouil Alexandros Fotakis:** Writing – original draft, Data curation. **Serena Battilomo:** Writing – review & editing, Data curation. **Daniele Petrone:** Writing – review & editing, Data curation. **Martina Del Manso:** Writing – review & editing, Data curation. **Antonino Bella:** Writing – review & editing, Data curation. **Flavia Riccardo:** Writing – review & editing, Funding acquisition. **Paola Stefanelli:** Writing – review & editing, Data curation. **Anna Teresa Palamara:** Writing – review & editing, Project administration. **Patrizio Pezzotti:** Writing – original draft, Methodology, Formal analysis, Conceptualization.

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.

Data availability

The authors do not have permission to share data.

Acknowledgements

This research was supported by the NextGenerationEU-MUR-PNRR Extended Partnership initiative on Emerging Infectious Diseases (project number PE00000007, INF-ACT).

Appendix A

Italian Integrated Surveillance of COVID-19 study group.

ISS coordination team: Antonino Bella, Stefano Boros, Marco Bressi, Emiliano Ceccarelli, Fortunato (Paolo) D'Ancona, Martina Del Manso, Corrado Di Benedetto, Massimo Fabiani, Antonietta Filia, Alberto Mateo Urdiales, Daniele Petrone, Patrizio Pezzotti, Flavia Riccardo, Maria Cristina Rota, Chiara Sacco, Paola Stefanelli, Giorgio Fedele, Luigina Ambrosio, Angela Di Martino, Marco Tallon, Maria Fenicia Vescio.

Regional representatives: Antonia Petrucci (Abruzzo); Michele La Bianca (Basilicata); Anna Domenica Mignuoli (Calabria); Pietro Buono (Campania); Erika Massimiliani (Emilia-Romagna); Fabio Barbone (Friuli Venezia Giulia); Francesco Vairo (Lazio); Camilla Sticchi (Liguria); Danilo Cereda (Lombardia); Marco Pompili (Marche); Francesco Sforza (Molise); Pierpaolo Bertoli (P.A. Bolzano); Pier Paolo Benetollo (P.A. Trento); Chiara Pasqualini (Piemonte); Lucia Bisceglia (Puglia); Maria Antonietta Palmas (Sardegna); Sebastiano Pollina Addario (Sicilia); Emanuela Balocchini (Toscana); Anna Tosti (Umbria); Mauro Ruffier (Valle D'Aosta); Filippo Da Re (Veneto).

Italian COVID-19 vaccines registry group.

Italian Ministry of Health: Serena Battilomo, Valeria Proietti.

Regional representatives: Camillo Odio (Abruzzo); Michele Recine (Basilicata); Innocenza Ruberto (Calabria); Salvatore Ascione e Massimo Bisogno (Campania); Gandolfo Miserendino, Massimiliano Navacchia (Emilia-Romagna); Beatrice Del Frate, Emanuela Cau (Friuli Venezia Giulia); Diego Baiocchi, Danilo Fusco (Lazio); Domenico Gallo (Liguria); Maria Rosa Marchetti (Lombardia); Liana Spazzafumo (Marche); Raffaele Malatesta (Molise); Antonio Fanolla (P.A. Bolzano); Diego Conforti, Carlo Trentini (P.A. Trento); Antonino Ruggeri (Piemonte); Concetta Ladalardo, Nehludoff Albano (Puglia); Marco Corona, Paolo Lombardi (Sardegna); Massimo Iacono (Sicilia); Paolo Bruno Angori, Andrea Belardinelli (Toscana); Milena Solfiti (Umbria); Stefano Fioraso (Valle D'Aosta); Chiara Poma, Nadia Raccanello (Veneto).

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.05.074.

References

[1] World Health Organization (WHO). WHO COVID-19 dashboard. Available from: https://data.who.int/dashboards/covid19/data?n=c (accessed 15 February 2024].
[2] 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.
[3] 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.
[4] Falsey AR, Sobieszczyk ME, Hirsch I, Sproule S, Robb ML, Corey L, et al. Phase 3 safety and efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 vaccine. N Engl J Med 2021;385(25):2348–60.
[5] Sadoff J, Gray G, Vandebosch A, 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] Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. N Engl J Med 2021;385(13):1172–83.
[7] Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. Lancet 2021;397(10286):1725–35.
[8] 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.
[9] Mateo-Urdiales A, Spila Alegiani S, Fabiani M, Pezzotti P, Filia A, Massari M, et al. Risk of SARS-CoV-2 infection and subsequent hospital admission and death at different time intervals since first dose of COVID-19 vaccine administration, Italy, 27 December 2020 to mid-April 2021. Eurosurveillance 2021;26(25):2100507.
[10] Menegale F, Manica M, Zardini A, Guzzetta G, Marziano V, d'Andrea V, et al. Evaluation of waning of SARS-CoV-2 vaccine-induced immunity: a systematic review and meta-analysis. JAMA Netw Open 2023;6(5):e2310650.

[11] Feikin DR, Higdon MM, Abu-Raddad LJ, Andrews N, Araos R, Goldberg Y, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. Lancet 2022;399 (10328):924–44.
[12] Willett BJ, Grove J, MacLean OA, Wilkie C, De Lorenzo G, Furnon W, et al. SARS-CoV-2 Omicron is an immune escape variant with an altered cell entry pathway. Nat Microbiol 2022;7(8):1161–79.
[13] Carabelli AM, Peacock TP, Thorne LG, Harvey WT, Hughes J, et al. SARS-CoV-2 variant biology: immune escape, transmission and fitness. Nat Rev Microbiol 2023; 21(3):162–77.
[14] European Medicines Agency (EMA). Adapted vaccine targeting BA.4 and BA.5 Omicron variants and original SARS-CoV-2 recommended for approval. Available from: https://www.ema.europa.eu/en/news/adapted-vaccine-targeting-ba4-and-ba5-omicron-variants-and-original-sars-cov-2-recommended-approval [accessed 15 February 2024].
[15] European Medicines Agency (EMA). EMA recommends approval of second adapted Spikevax vaccine. Available from: https://www.ema.europa.eu/en/news/ema-recommends-approval-second-adapted-spikevax-vaccine [accessed 15 February 2024].
[16] Italian Ministry of Health (MoH) and Italian Medicine Agency (AIFA). Aggiornamento delle indicazioni sull'utilizzo dei vaccini a m-RNA bivalenti. Available from: https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2022&codLeg=89142&parte=1%20&serie=null [accessed 15 February 2024].
[17] Italian National Institute of Statistics (Istat). Demography in figures – Resident population. Available from: https://demo.istat.it/app/?i=POS&a=2022&l=en [accessed 5 February 2024].
[18] GitHub. COVID-19 Opendata Vaccini. Available from: https://github.com/italia/covid19-opendata-vaccini [accessed 15 February 2024].
[19] Italian Government, Presidency of the Council of Ministers. Data repository. Available from: https://www.governo.it/it/dipartimenti/commissario-straordinario-lemergenza-covid-19/15974 [accessed 15 February 2024].
[20] Italian National Institute of Health, EpiCentro. Epidemiology for public health - COVID-19 integrated surveillance: key national data. Available from: https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-integrated-surveillance-data [accessed 15 February 2024].
[21] Italian National Institute of Statistics (Istat). Life tables. Available from: http://dati.istat.it/Index.aspx?lang=en&SubSessionId=d6cfb2ad-4b0e-43c5-bb3f-50ec50cbc3e4 [accessed 15 February 2024].
[22] Italian National Institute of Statistics (Istat). Principali statistiche geografiche sui Comuni – classificazioni statistiche e dimensioni dei Comuni. Available from: https://www.istat.it/it/archivio/156224 [accessed 15 February 2024].
[23] Rosano A, Pacelli B, Zengarini N, Costa G, Cislaghi C, Caranci N. Aggiornamento e revisione dell'indice di deprivazione italiano 2011 a livello di sezione di censimento. Epidemiol Prev 2020;44(2–3):162–70.
[24] European Centre for Disease Prevention and Control (ECDC). Data on SARS-CoV-2 variants in the EU/EAA. Available from: https://www.ecdc.europa.eu/en/publications-data/data-virus-variants-covid-19-eueea [accessed 15 February 2024].
[25] World Health Organization (WHO). International guidelines for certification and classification (coding) of COVID-19 as cause of death. Available from: https://www.who.int/publications/m/item/international-guidelines-for-certification-and-classification-(coding)-of-covid-19-as-cause-of-death [accessed 15 February 2024].
[26] Bonmarin I, Belchior E, Lévy-Bruhl D. Impact of influenza vaccination on mortality in the French elderly population during the 2000–2009 period. Vaccine 2015;33 (9):1099–101.
[27] Machado A, Mazagatos C, Dijkstra F, Kislaya I, Gherasim A, McDonald SA, et al. Impact of influenza vaccination programmes among the elderly population on primary care, Portugal, Spain and the Netherlands: 2015/16 to 2017/18 influenza seasons. Euro Surveill 2019 Nov;24(45):1900268.
[28] European Centre for Disease Prevention and Control (ECDC). Interim public health considerations for COVID-19 vaccination roll-out during 2023. Available from: https://www.ecdc.europa.eu/en/publications-data/interim-public-health-considerations-covid-19-vaccination-roll-out-during-2023 [accessed 15 February 2024].
[29] Madhi SA, Feikin DR. Are bivalent vaccines better than ancestral-virus monovalent vaccines in protecting against severe omicron COVID-19? Lancet Infect Dis 2023; 12:1325–7.
[30] Kurhade C, Zou J, Xia H, Liu M, Chang HC, Ren P, et al. Low neutralization of SARS-CoV-2 Omicron BA.2.75.2, BQ.1.1 and XBB.1 by parental mRNA vaccine or a BA.5 bivalent booster. Nat Med 2023;29(2):344–7.
[31] Davis-Gardner ME, Lai L, Wali B, Samaha H, Solis D, Lee M, et al. Neutralization against BA.2.75.2, BQ.1.1, and XBB from mRNA Bivalent Booster. N Engl J Med 2023;388(2):183–5.
[32] Antunes L, Mazagatos C, Martínez-Baz I, Gomez V, Borg ML, Petrović G, et al. Effectiveness of the adapted bivalent mRNA COVID-19 vaccines against hospitalisation in individuals aged ≥ 60 years during the Omicron XBB lineage-predominant period: VEBIS SARI VE network, Europe, February to August, 2023. Euro Surveill 2024;29(3):2300708.
[33] Kirsebom FCM, Harman K, Lunt RJ, Andrews N, Groves N, Abdul Aziz N, et al. Vaccine effectiveness against hospitalisation estimated using a test-negative case-control study design, and comparative odds of hospital admission and severe outcomes with COVID-19 sub-lineages BQ.1, CH.1.1. and XBB.1.5 in England. Lancet Reg Health Eur 2023;35:100755.
[34] Brockman MA, Mwimanzi F, Lapointe HR, Sang Y, Agafitei O, Cheung PK, et al. Reduced magnitude and durability of humoral immune responses to COVID-19 mRNA vaccines among older adults. J Infect Dis 2022;225(7):1129–40.
[35] Hansen CH. Bias in vaccine effectiveness studies of clinically severe outcomes that are measured with low specificity: the example of COVID-19-related hospitalisation. Euro Surveill 2024;29(7):2300259.