**Estimating all-cause deaths averted in the first two years of the COVID-19 vaccination campaign in Italy**

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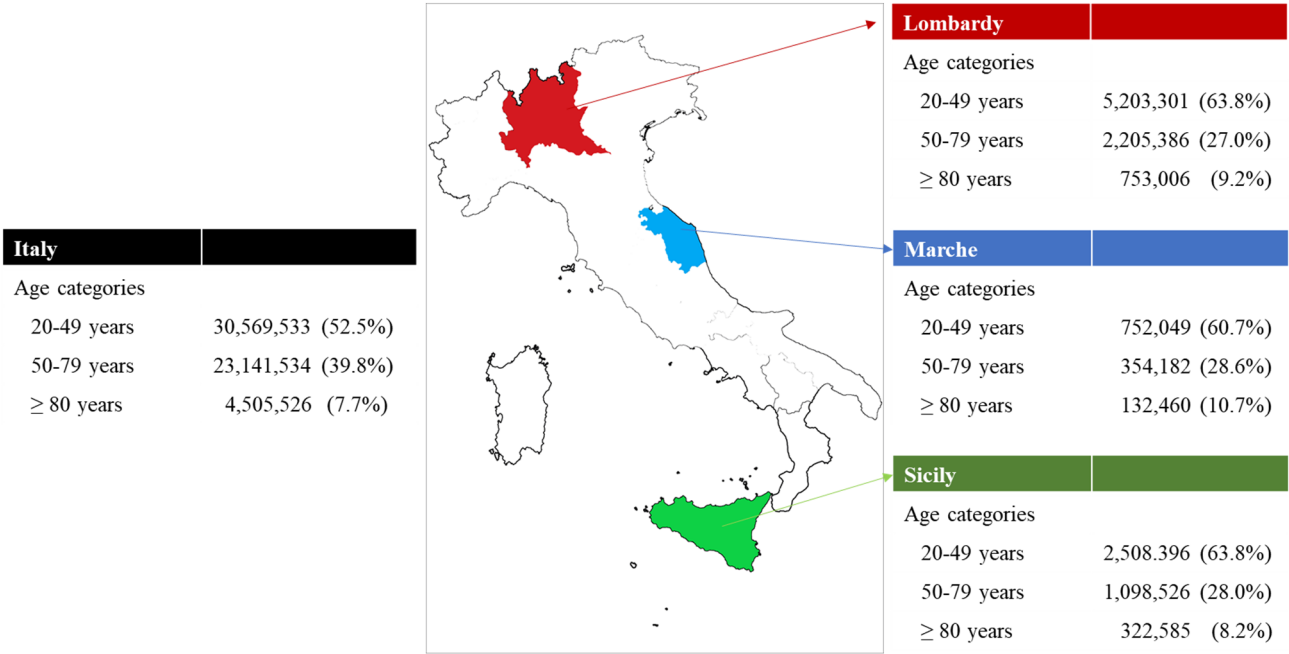
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**Annex S1. Localization and age structure (January, 2021) of citizens from the three Italian Regions involved in the current study, compared with the entire Italian population.**



| Lombardy | |
|---|---|
| Age categories | |
| 20-49 years | 5,203,301 (63.8%) |
| 50-79 years | 2,205,386 (27.0%) |
| ≥ 80 years | 753,006 (9.2%) |

| Marche | |
|---|---|
| Age categories | |
| 20-49 years | 752,049 (60.7%) |
| 50-79 years | 354,182 (28.6%) |
| ≥ 80 years | 132,460 (10.7%) |

| Sicily | |
|---|---|
| Age categories | |
| 20-49 years | 2,508.396 (63.8%) |
| 50-79 years | 1,098,526 (28.0%) |
| ≥ 80 years | 322,585 (8.2%) |

| Italy | |
|---|---|
| Age categories | |
| 20-49 years | 30,569,533 (52.5%) |
| 50-79 years | 23,141,534 (39.8%) |
| ≥ 80 years | 4,505,526 (7.7%) |

**Annex S2. Seasonal autoregressive integrated moving average with exogenous factors (SARIMAX) modelling excess mortality.**

Excess mortality was defined as the difference between the observed and benchmark death counts. While the observed mortality was the actual death count during the vaccinal period (i.e., from December 2020 until October 2022), the benchmark mortality was defined as the estimated death count according to historical trends, excluding the influence of COVID-19 (i.e., during the years 2015-2019). In other words, the expected death count during the vaccinal period provided that the mortality process exhibited a "natural variability" as that of the no-COVID period (the benchmark based on the counterfactual condition of COVID-19).

The ARIMA (autoregressive integrated moving average) model, which uses auto-regression and moving average, and incorporates a differencing order to remove trend and/or seasonality [1], is one of the most widely used statistical methods for forecasting stationary time series [2].

Particularly, because the time process of interest (daily count of all-cause deaths) forms a time series with seasonal variations, an extension of ARIMA, the so-called SARIMA (seasonal ARIMA) was used in this study [3-7]. In addition, besides seasons, other exogenous factors likely affect the time process of interest (e.g., the environmental temperature); therefore, a SARIMAX (seasonal autoregressive integrated moving average with exogenous factors) model was fitted for estimating the expected death count ($X_t$). SARIMAX assumes the following form:

$$X_t = \beta_0 + \beta_0 X_t^{(1)} + m_t + s_t + Y_t$$

where $\beta_0$ indicates the intercept and $\beta_0 X_t^{(1)}$, $m_t$, $s_t$, and $Y_t$ the effects of exogenous factors (in our case, the temperature at time $t$), trend, season, and noise, respectively.

The ARIMA model contains 3 parameters ($p$, $d$, $q$): (i) parameter $p$ represents the periods to lag for; (ii) parameter $d$ represents the number of differencing transformations done to remove trend and/or seasonality therefore turning the time-series into a stationary one, i.e, making the mean and variance constant over time; (iii) parameter $q$ represents the lag of the error component of the ARIMA model, which is the part of the time-series that cannot be explained by trend or seasonality. Selecting appropriate values for parameters $p$ and $q$ requires testing and optimization. To choose the values, one must inspect visual observations of the data to determine trend and/or seasonality in the form of auto-correlation function (ACF) and partial auto-correlation function (PACF) charts [1].

In our study, the input variables were measured during the control period from January 1, 2015, to December 31, 2019, and included the time series of daily observed deaths reported by the Italian National Institute of Statistics [8] stratified by Italian region and age category, and the daily temperatures tracked by the Italian National Environmental Protection System official site [9].

Selection of the parameters to be set in the SARIMAX model was performed by using the "auto.arima" package of the 4.0.2 version of the R statistical software, which returns the best results based on the values of the Akaike's Information Criterion (AIC), corrected AIC (AICc) or Bayesian Information Criteria (BIC). Specifically, using the "auto.arima" package, these values were used to compare the models in terms of quality, which is achieved by finding a balance between the fit of the model and its complexity [1].

**Annex S3**. **Modelling the prevented fraction.**

**Notations**

d  generic day of the vaccinal period, with d=0,….,d=D; that is, from February 1, 2021 (14 days after the first Italian citizen completed the first COVID-19 vaccine dose) to October 31, 2022 (the last date with available data for the current paper)

r  Italian region, with $r$ = 1, 2, and 3 for citizens from Lombardy, Marche, and Sicily, respectively

a  age category, with $a$ = 1, 2, and 3 for citizens aged 20-49, 50-79, and 80 years or older, respectively

v  vaccine dose, with $v$ = 1, 2, or 3 indicating the first complete dose, and the first and second booster doses, respectively

j  days elapsed since receiving the last vaccine dose, with j=1,…,J

s  viral original (v=0) or Omicron (v=1) variant of SARS-CoV-2

**Remarks**

The cumulative prevented fraction (PF) from February 1, 2021, was calculated from:

$$PF_{rad} = \sum_{v=1}^{3} \sum_{j=1}^{J} PV_{ravd} \times VE_{avjd}$$

The first quantity, $PV_{ravd}$, indicates the cumulative prevalence of citizens resident in each region, belonging to a given age category, reached by a given dose of vaccine, each day $d$ of the vaccinal period. Under the assumption that clinically significant immunity is achieved two weeks after receiving the vaccine [10], we moved the effective date of vaccine administration for counting the daily number of vaccinated forward by 14 days. Because $PV_{ra1d}$, $PV_{ra2d}$, and $PV_{ra3d}$ included citizens who received the (i) first dose (but not the second and third ones), (ii) second dose (but not the third one), and (iii) third dose, respectively, exposure to one, two, or three doses is to be considered mutually exclusive and independent.

The second quantity, $VE_{avjs}$, indicates the estimated vaccine effectiveness (VE) in avoiding deaths. VE is assumed to be invariant between regions, but heterogeneous according with age, dose, time elapsed since vaccination, and prevalent viral strain. To model VE according to these parameters, we proceeded as follows:

First, a systematic review and meta-analysis was conducted to summarize meta-analytic estimates of VE according to age and dose. We searched PubMed to November 15, 2022, for observational studies reporting estimates of VE against death, stratified by age and vaccine dose, of the two mRNA-based (manufactured by Pfizer and Moderna) and two adenovirus-vectored (manufactured by Oxford-AstraZeneca and Janssen) vaccines available in Italy. Out of 961 original papers and 7 systematic reviews, 19 research articles were included in the final meta-analysis [11-29]. Among these, 17, 5, and 3 reported age-specific VE estimates for the first, second, and third dose, respectively. The following table shows the random effect meta-analytic estimates of VE among strata of age and vaccine dose:

| | Meta-analytic (pooled) estimate of VE and 95% Confidence Interval | Number of studies considered |
|---|---|---|
| Age 20-49 years | | |
| 1 dose | 87% (81% - 90%) | 3 |
| 2 doses | Not available | 0 |
| 3 doses | Not available | 0 |
| Age 50-79 years | | |
| 1 dose | 94% (91% - 95%) | 19 |
| 2 doses | 96% (93% - 98%) | 4 |
| 3 doses | 91% (66% - 98%) | 2 |
| Age 80+ years | | |
| 1 dose | 80% (79% - 82%) | 20 |
| 2 doses | 86% (74% - 92%) | 4 |
| 3 doses | 81% (76% - 86%) | 3 |

Since, to the best of our knowledge, estimates of the second and third dose effects in people aged less than 50 years are not available, the summarized VE for people aged 50 to 79 years (that is, 96% and 91%) were used.

Second, with the aim of considering the waning of VE over time, we considered data from a published population-based study conducted on more than 9 million beneficiaries of the Lombardy Regional Health Service [30], having the same setting of one of the 3 regions considered in the current study. Particularly, we extracted the monthly VE values against severe COVID-19 illness, and we evaluated the decrease over time. Starting from these data, we fitted a second-degree polynomial function to predict the daily VE decline from 14 days to nine months after vaccine administration. The polynomial function assumed the following form: $VE_j = 1 - (0.186 - 0.00151 \times j + 0.000014 \times j^2)$.

Finally, to account for the reduced effectiveness of mRNA and viral-vector vaccines in epidemic periods led by different SARS-CoV-2 variants, summarized estimates from four systematic reviews of the literature on this topic [31-34] and two additional original papers [35,36], lead of considering decreased VE values of 5% starting from January 2022, the month when the Omicron variant became dominant in Italy [37].

Finally, the overall cumulative prevented fraction in each region according to the vaccination speed in reaching citizens with one, two, and three vaccine doses was calculated, net of between-region differences in age structure, by applying the direct standardization:

$$FP_r = \sum_{v=1}^{3} \sum_{a=1}^{3} FP_{ra} \times p'_a$$

where p'$_a$ indicates the proportion of Italian citizens belonging to a given age category, with respect to Italian citizens aged 20 years or older (Supplemental Material, **Annex S1**, reports the corresponding values).

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**Annex S4**. **Sensitivity analyses (methods).**

### Sensitivity analysis 1

The following values of vaccine effectiveness (VE) specific for each age category and vaccinal dose was assumed as an alternative to those used for the main analysis (**Annex S3**):

|  | Meta-analytic (summarized) estimate of VE |
|---|---|
| Age 20-49 years |  |
| 1 dose | 87% |
| 2 doses | 96% |
| 3 doses | 96% |
| Age 50-79 years |  |
| 1 dose | 94% |
| 2 doses | 96% |
| 3 doses | 96% |
| Age 80+ years |  |
| 1 dose | 80% |
| 2 doses | 86% |
| 3 doses | 86% |

VE: vaccine effectiveness

### Sensitivity analysis 2

A 1% decrease in VE starting from January 2022 (i.e., when the Omicron variant became dominant in Italy) was assumed instead of 5% as in the main analysis.

### Sensitivity analysis 3

Values of VE specific for each age category and vaccinal dose as in sensitivity analysis 1 and a 1% decrease in VE starting from January 2022 (when Omicron variant became dominant in Italy) was assumed instead of 5% as in the main analysis.

**Annex S5**. Number of positive swabs (Supplementary Table S1) and number of vaccination doses inoculated over time (Supplementary Table S2) in the three Regions.

**Supplementary Table S1**

| Period | Lombardy | Marche | Sicily |
|---|---|---|---|
| December 2020 | 6,948 | 1,927 | 4,028 |
| January 2021 | 59,151 | 13,863 | 42,459 |
| February 2021 | 65,027 | 12,370 | 16,455 |
| March 2021 | 132,433 | 20,289 | 21,565 |
| April 2021 | 69,136 | 9,559 | 34,364 |
| May 2021 | 30,497 | 4,977 | 17,322 |
| June 2021 | 6,708 | 958 | 5,887 |
| July 2021 | 11,145 | 1,922 | 11,244 |
| August 2021 | 16,724 | 4,955 | 33,590 |
| September 2021 | 14,050 | 3,340 | 21,530 |
| October 2021 | 10,839 | 2,375 | 9,856 |
| November 2021 | 37,961 | 7,627 | 15,503 |
| December 2021 | 284,790 | 21,605 | 48,146 |
| January 2022 | 911,717 | 115,447 | 249,480 |
| February 2022 | 203,479 | 66,254 | 152,679 |
| March 2022 | 204,667 | 63,411 | 150,579 |
| April 2022 | 228,126 | 54,014 | 118,791 |
| May 2022 | 127,540 | 28,936 | 68,678 |
| June 2022 | 158,400 | 25,621 | 85,771 |
| July 2022 | 319,875 | 76,225 | 184,424 |
| August 2022 | 102,225 | 29,386 | 61,862 |
| September 2022 | 100,108 | 18,232 | 29,465 |
| October 2022 | 209,057 | 31,082 | 38,363 |

**Supplementary Table S2**

| Period | Lombardy | | | | Marche | | | | Sicily | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No vaccine | 1 dose | 2 doses | 3 doses | No vaccine | 1 dose | 2 doses | 3 doses | No vaccine | 1 dose | 2 doses | 3 doses |
| December 2020 | 100.0% | 0.0% | 0.0% | 0.0% | 100.0% | 0.0% | 0.0% | 0.0% | 100.0% | 0.0% | 0.0% | 0.0% |
| January 2021 | 99.1% | 0.9% | 0.0% | 0.0% | 98.8% | 1.2% | 0.0% | 0.0% | 98.4% | 1.6% | 0.0% | 0.0% |
| February 2021 | 96.9% | 3.1% | 0.0% | 0.0% | 97.6% | 2.4% | 0.0% | 0.0% | 97.2% | 2.8% | 0.0% | 0.0% |
| March 2021 | 93.5% | 6.5% | 0.0% | 0.0% | 92.0% | 8.0% | 0.0% | 0.0% | 94.0% | 6.0% | 0.0% | 0.0% |
| April 2021 | 88.1% | 11.9% | 0.0% | 0.0% | 87.6% | 12.4% | 0.0% | 0.0% | 88.7% | 11.3% | 0.0% | 0.0% |
| May 2021 | 75.0% | 25.0% | 0.0% | 0.0% | 75.2% | 24.8% | 0.0% | 0.0% | 77.1% | 22.9% | 0.0% | 0.0% |
| June 2021 | 65.3% | 34.7% | 0.0% | 0.0% | 64.6% | 35.4% | 0.0% | 0.0% | 65.7% | 34.3% | 0.0% | 0.0% |
| July 2021 | 36.5% | 63.5% | 0.0% | 0.0% | 38.4% | 61.6% | 0.0% | 0.0% | 44.0% | 56.0% | 0.0% | 0.0% |
| August 2021 | 27.2% | 72.8% | 0.0% | 0.0% | 30.5% | 69.5% | 0.0% | 0.0% | 36.9% | 63.1% | 0.0% | 0.0% |
| September 2021 | 20.3% | 79.5% | 0.2% | 0.0% | 24.5% | 75.3% | 0.2% | 0.0% | 29.7% | 70.2% | 0.1% | 0.0% |
| October 2021 | 17.2% | 79.5% | 3.4% | 0.0% | 21.2% | 76.1% | 2.7% | 0.0% | 25.6% | 73.0% | 1.4% | 0.0% |
| November 2021 | 15.9% | 69.9% | 14.1% | 0.0% | 19.4% | 66.7% | 14.0% | 0.0% | 23.3% | 67.6% | 9.1% | 0.0% |
| December 2021 | 15.3% | 40.6% | 44.1% | 0.0% | 18.5% | 41.8% | 39.8% | 0.0% | 22.0% | 49.4% | 28.6% | 0.0% |
| January 2022 | 14.5% | 14.4% | 71.1% | 0.0% | 17.3% | 16.4% | 66.3% | 0.0% | 20.2% | 24.5% | 55.4% | 0.0% |
| February 2022 | 13.6% | 7.8% | 78.6% | 0.0% | 16.3% | 11.6% | 72.1% | 0.0% | 17.9% | 18.8% | 63.3% | 0.0% |
| March 2022 | 13.4% | 5.5% | 81.0% | 0.1% | 15.9% | 9.7% | 74.3% | 0.1% | 17.0% | 16.8% | 66.1% | 0.0% |
| April 2022 | 13.3% | 4.5% | 81.4% | 0.8% | 15.8% | 8.9% | 74.8% | 0.5% | 16.9% | 16.0% | 66.9% | 0.2% |
| May 2022 | 13.3% | 4.0% | 80.6% | 2.1% | 15.8% | 8.7% | 74.4% | 1.1% | 16.8% | 15.6% | 66.9% | 0.6% |
| June 2022 | 13.3% | 3.5% | 80.5% | 2.7% | 15.8% | 8.5% | 74.3% | 1.4% | 16.8% | 15.4% | 66.9% | 0.9% |
| July 2022 | 13.3% | 3.0% | 78.2% | 5.5% | 15.8% | 8.2% | 72.9% | 3.0% | 16.8% | 15.1% | 66.0% | 2.2% |
| August 2022 | 13.3% | 2.8% | 76.8% | 7.1% | 15.8% | 8.1% | 71.9% | 4.3% | 16.8% | 14.9% | 65.7% | 2.6% |
| September 2022 | 13.3% | 2.7% | 75.9% | 8.2% | 15.8% | 8.0% | 71.4% | 4.8% | 16.7% | 14.8% | 65.5% | 2.9% |
| October 2022 | 13.3% | 2.5% | 72.4% | 11.9% | 15.7% | 7.9% | 69.4% | 7.0% | 16.7% | 14.7% | 64.5% | 4.0% |

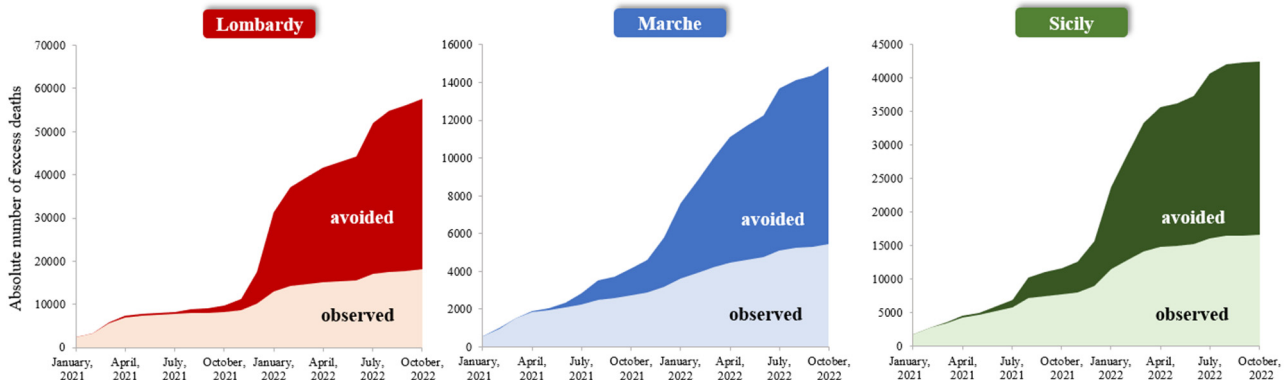**Annex S6**. **Sensitivity analyses (results).**

**Sensitivity analysis 1**

Different values of vaccine effectiveness (VE) specific for each age category and vaccinal dose was assumed as an alternative to those used for the main analysis.

**Supplementary Figure S1.** Daily time series of the prevented fraction from January 01, 2021, to October 31, 2022, in the Italian regions of Lombardy, Marche, and Sicily.
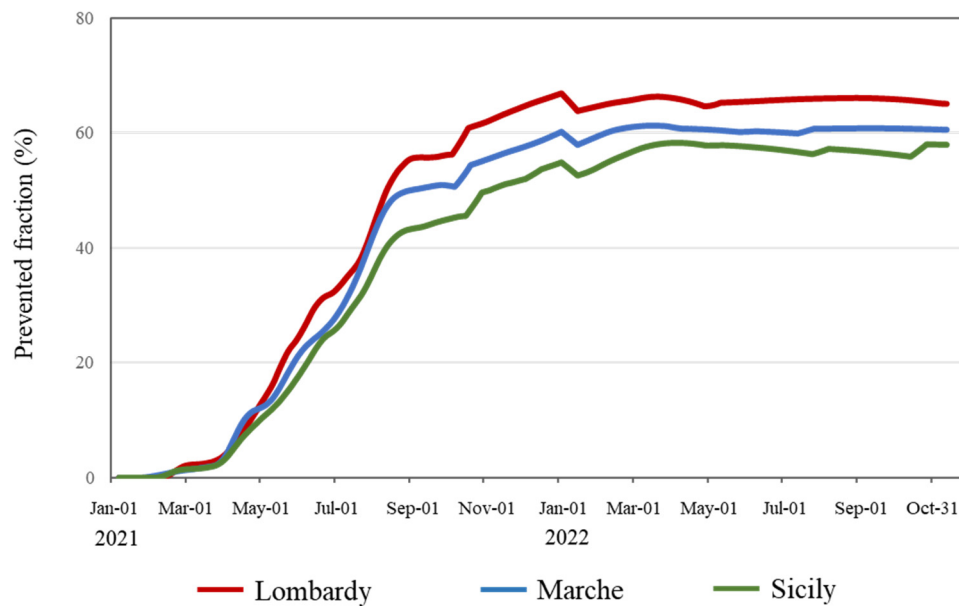


**Supplementary Figure S2.** Daily time series of the cumulative number of excess deaths (i) observed (net of seasonality and temperature); (ii) avoided; and (iii) would have occurred without vaccination (obtained by considering the first and second quantities together) in the Italian regions of Lombardy, Marche, and Sicily.
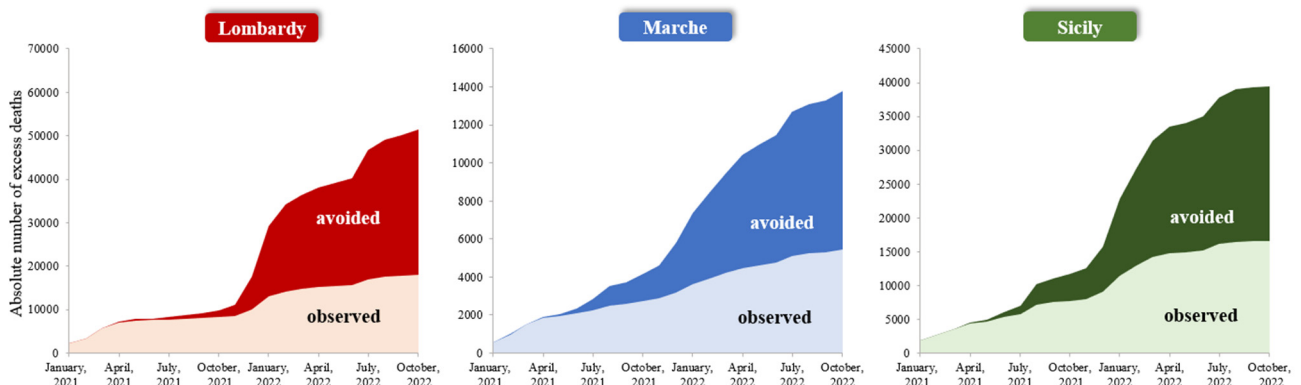
## Sensitivity analysis 2

A 1% decrease in VE starting from January 2022 (i.e., when the Omicron variant became dominant in Italy) was assumed instead of 5% as in the main analysis.

**Supplementary Figure S3.** Daily time series of the prevented fraction from January 01, 2021, to October 31, 2022, in the Italian regions of Lombardy, Marche, and Sicily.
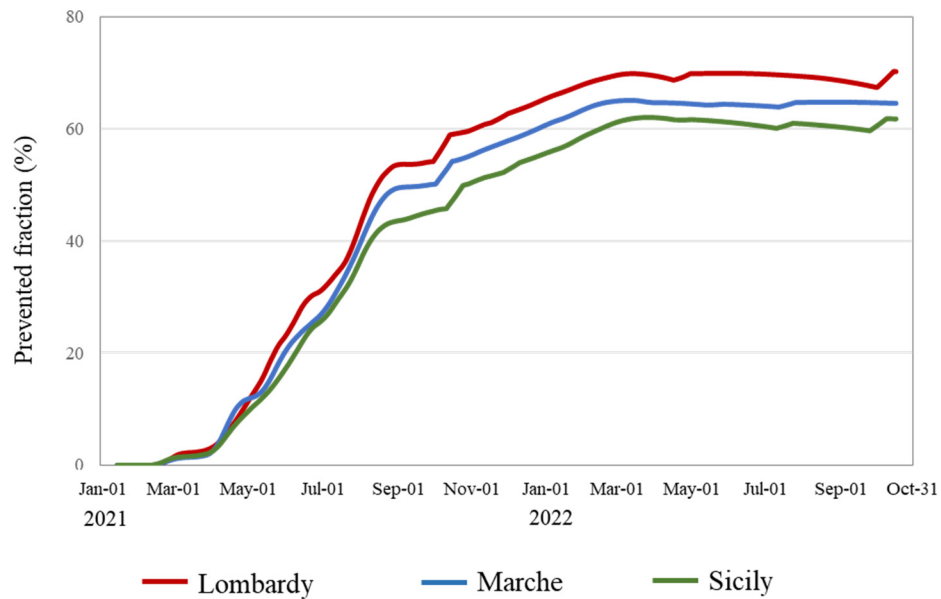


**Supplementary Figure S4.** Daily time series of the cumulative number of excess deaths (i) observed (net of seasonality and temperature); (ii) avoided; and (iii) would have occurred without vaccination (obtained by considering the first and second quantities together) in the Italian regions of Lombardy, Marche, and Sicily.

**Sensitivity analysis 3**

Values of VE specific for each age category and vaccinal dose as in sensitivity analysis 1 and a 1% decrease in VE starting from January 2022 (when Omicron variant became dominant in Italy) was assumed instead of 5% as in the main analysis.

**Supplementary Figure S5.** Daily time series of the prevented fraction from January 01, 2021, to October 31, 2022, in the Italian regions of Lombardy, Marche, and Sicily.



**Supplementary Figure S6.** Daily time series of the cumulative number of excess deaths (i) observed (net of seasonality and temperature); (ii) avoided; and (iii) would have occurred without vaccination (obtained by considering the first and second quantities together) in the Italian regions of Lombardy, Marche, and Sicily.