We measured vaccine effectiveness (VE) against COVID-19-related severe outcomes in elderly people in Portugal between May and July 2022. In ≥ 80 year-olds, the second booster dose VE was 81% (95% CI: 75–85) and 82% (95% CI: 77–85), respectively, against COVID-19-related hospitalisation and death. The first booster dose VE was 63% (95% CI: 55–70) in ≥ 80 year-olds and 74% (95% CI: 66–80) in 60–79 year-olds against hospitalisation, and 63% (95% CI: 57–69) and 65% (95% CI: 54–74) against death.

Since 15 May 2022, a second booster dose of the coronavirus disease (COVID-19) mRNA vaccine has been rolled out in Portugal for those 80 years and older or residents in long-term care facilities [1], according to the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA) recommendations issued in April 2022 [2]. In July 2022, following the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron (Phylogenetic Assignment of Named Global Outbreak Lineages (Pangolin) designation B.1.1.529) BA.5 variant across Europe, ECDC and EMA extended the recommendation of the second booster dose to the population aged 60–79 years [3]. However, at the time of this study, this extension has not yet been implemented in Portugal.

We aimed to estimate vaccine effectiveness (VE) of the second booster dose against COVID-19-related hospitalisation and death in the population in Portugal 80 years and older during Omicron BA.5 circulation, from 15 May to 31 July 2022. As a secondary objective, we present VE of the primary series and the first booster dose against COVID-19-related severe outcomes in those aged 60 years and older.

**Study design**

We carried out a study based on linkage of electronic health records using the National Health Service User (NHSU) unique numeric identifier to link the databases [4]. The study period covered the period of circulation of Omicron BA.5 [5], from 15 May 2022, when the second booster began to be administrated, to 31 July 2022. The target population included residents in Portugal mainland, aged 60 years and older and eligible for COVID-19 vaccination.

Exclusion criteria were: age registered as more than 110 years, documented SARS-CoV-2 infection within 90 days before the start of the follow-up, being vaccinated with vaccines other than those recommended in Portugal, having an interval between doses other than recommended and not having any contact with the national healthcare service in the past 3 years. We estimated the VE separately for two cohorts: age 60–79 years and ≥ 80 years.

**Outcomes definitions**

COVID-19-related hospitalisation was defined as admission to a hospital for at least 24 h, following laboratory-confirmed infection with SARS-CoV-2 and having COVID-19 as the primary diagnosis at discharge (ICD10 coding U071).

COVID-19-related death was defined as death for which COVID-19 was recorded as the cause of death (U071) or deaths that occurred within 30 days after
|                                | Unvaccinated (n = 51,411) | Primary series (n = 44,284) | First booster (n = 204,362) | Second booster (n = 342,010) |
|--------------------------------|---------------------------|----------------------------|-----------------------------|----------------------------|
| **Age in years, median (IQR)** | 86.0 (82.0–90.0)          | 85.0 (82.0–88.0)           | 84.0 (82.0–88.0)            | 84.0 (82.0–88.0)            |
| **Age group (years)**          |                           |                            |                            |                            |
| 80–84                          | 21,320 41.5               | 20,930 47.3                | 106,473 52.1               | 175,554 51.3               |
| 85–89                          | 16,285 31.7               | 14,838 33.5                | 65,368 32.0                | 113,156 33.1               |
| 90–94                          | 9,410 18.3                | 6,614 14.9                 | 25,967 12.7                | 43,222 12.6                |
| ≥ 95                           | 4,396 8.6                 | 1,902 4.3                  | 6,554 3.2                  | 10,078 2.9                 |
| **Male sex**                   | 18,065 35.1               | 14,080 31.8                | 74,941 36.7                | 138,906 40.6               |
| **Region**                     |                           |                            |                            |                            |
| ARS Alentejo                   | 2,315 4.5                 | 2,565 5.8                  | 12,558 6.1                 | 19,618 5.7                 |
| ARS Algarve                    | 3,941 7.7                 | 3,190 7.2                  | 9,922 4.9                  | 13,141 3.8                 |
| ARS Centro                     | 9,275 18.0                | 8,455 19.1                 | 41,654 20.4                | 68,354 20.0                |
| ARS LVT                        | 18,036 35.1               | 16,513 37.3                | 74,848 36.6                | 120,956 35.4               |
| ARS Norte                      | 11,785 22.9               | 13,054 29.5                | 64,190 31.4                | 118,863 34.8               |
| Missing                        | 6,059 11.8                | 507 1.1                    | 1,190 0.6                  | 1,078 0.3                  |
| **European deprivation index quintile** |                       |                            |                            |                            |
| Q1 (least deprived)            | 6,462 12.6                | 5,975 13.5                 | 32,086 15.7                | 56,305 16.5                |
| Q2                             | 6,524 12.7                | 6,266 14.1                 | 31,689 15.5                | 51,919 15.2                |
| Q3                             | 6,336 12.3                | 6,192 14.0                 | 29,000 14.2                | 50,771 14.8                |
| Q4                             | 12,445 24.2               | 12,226 27.6                | 57,324 28.1                | 97,586 28.5                |
| Q5 (most deprived)             | 13,585 26.4               | 13,118 29.6                | 53,073 26.0                | 84,351 24.7                |
| Missing                        | 6,059 11.8                | 507 1.1                    | 1,190 0.6                  | 1,078 0.3                  |
| **Number of chronic diseases** |                           |                            |                            |                            |
| 0                              | 20,039 39.0               | 7,012 15.8                 | 26,410 12.9                | 39,716 11.6                |
| 1                              | 10,846 21.1               | 9,491 21.4                 | 40,555 19.8                | 66,821 19.5                |
| 2                              | 9,411 18.3                | 10,897 24.6                | 51,631 25.3                | 87,130 25.5                |
| 3                              | 6,168 12.0                | 8,395 19.0                 | 42,510 20.8                | 73,868 21.6                |
| 4                              | 3,091 6.0                 | 5,048 11.4                 | 25,607 12.5                | 44,013 12.9                |
| ≥ 5                            | 1,856 3.6                 | 3,441 7.8                  | 17,649 8.6                 | 30,462 8.9                 |
| **Number of SARS-CoV-2 tests** |                           |                            |                            |                            |
| 0                              | 36,601 71.2               | 17,492 39.5                | 75,411 36.9                | 148,877 43.5               |
| 1                              | 6,657 12.9                | 8,834 19.9                 | 43,415 21.2                | 69,375 20.3                |
| 2                              | 3,068 6.0                 | 5,222 11.8                 | 26,217 12.8                | 42,123 12.3                |
| 3                              | 1,708 3.3                 | 3,224 7.3                  | 16,536 8.1                 | 25,322 7.4                 |
| 4–9                            | 2,802 5.5                 | 7,399 16.7                 | 34,249 16.8                | 47,183 13.8                |
| ≥ 10                           | 575 1.1                   | 2,113 4.8                  | 8,534 4.2                  | 9,130 2.7                  |
| Any other vaccine uptakea      | 8,610 16.7                | 23,952 54.1                | 168,146 82.3               | 311,662 91.1               |

ARS: regional health administration; COVID-19: coronavirus disease; LVT: Lisbon and Tagus Valley; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

a Received at least one of the following vaccines since 2017, influenza vaccine, pneumococcal conjugate vaccines (PCV13, PCV7 or PCV10) and pneumococcal polysaccharide vaccine (PPSV23).
Table 2
Participants’ characteristics at baseline by exposure status at the end of the follow-up period, age cohort 60–79 years, COVID-19 vaccine effectiveness study, Portugal, 15 May–31 July 2022 (n = 1,984,107)

|                          | Unvaccinated (n = 147,512) | Primary series (n = 220,699) | First booster (n = 1,615,896) |
|--------------------------|-----------------------------|------------------------------|-------------------------------|
|                          | n                           | n                            | n                            |
| Age in years, median (IQR) | 68.0 (63.0–73.0)            | 67.0 (63.0–72.0)             | 69.0 (65.0–74.0)             |
| Age group                |                             |                              |                              |
| 60–64                    | 49,832 (33.8)               | 78,648 (35.6)                | 402,090 (24.9)               |
| 65–69                    | 37,828 (25.6)               | 58,750 (26.6)                | 451,544 (27.9)               |
| 70–74                    | 33,054 (22.4)               | 47,360 (21.5)                | 438,185 (27.1)               |
| 75–79                    | 26,798 (18.2)               | 35,941 (16.3)                | 324,077 (20.1)               |
| Male sex                 | 69,802 (47.3)               | 98,113 (44.5)                | 733,873 (45.4)               |
| Region                   |                             |                              |                              |
| ARS Alentejo             | 5,626 (3.8)                 | 8,917 (4.0)                  | 78,900 (4.9)                 |
| ARS Algarve              | 15,324 (10.4)               | 13,240 (6.0)                 | 75,145 (4.7)                 |
| ARS Centro               | 22,902 (15.5)               | 35,640 (16.1)                | 288,851 (17.9)               |
| ARS LVT                  | 52,152 (35.4)               | 76,948 (34.9)                | 556,184 (34.4)               |
| ARS Norte                | 32,406 (22.0)               | 83,339 (37.8)                | 608,265 (37.6)               |
| Missing                  | 19,102 (12.9)               | 2,615 (1.2)                  | 8,551 (0.5)                  |
| European deprivation index quintile |            |                              |                              |
| Q1 (least deprived)      | 16,777 (11.4)               | 28,032 (12.7)                | 238,864 (14.8)               |
| Q2                       | 17,048 (11.6)               | 30,038 (13.6)                | 241,030 (14.9)               |
| Q3                       | 16,564 (11.2)               | 31,766 (14.4)                | 238,676 (14.8)               |
| Q4                       | 34,792 (23.6)               | 62,347 (28.2)                | 464,215 (28.7)               |
| Q5 (most deprived)       | 43,229 (29.3)               | 65,901 (29.9)                | 424,560 (26.3)               |
| Missing                  | 19,102 (12.9)               | 2,615 (1.2)                  | 8,551 (0.5)                  |
| Number of chronic diseases |                             |                              |                              |
| 0                        | 81,499 (55.2)               | 65,604 (29.7)                | 421,596 (26.1)               |
| 1                        | 31,436 (21.3)               | 55,312 (25.1)                | 420,812 (26.0)               |
| 2                        | 19,093 (12.9)               | 47,571 (21.6)                | 378,138 (23.4)               |
| 3                        | 9,613 (6.5)                 | 30,688 (13.9)                | 239,821 (14.8)               |
| 4                        | 4,034 (2.7)                 | 14,192 (6.4)                 | 105,436 (6.5)                |
| > 5                      | 1,837 (1.2)                 | 7,332 (3.3)                  | 49,993 (3.1)                 |
| Number of SARS-CoV-2 tests |                             |                              |                              |
| 0                        | 86,350 (58.5)               | 49,951 (22.6)                | 601,190 (37.2)               |
| 1                        | 26,439 (17.9)               | 50,811 (23.0)                | 360,039 (22.3)               |
| 2                        | 13,366 (9.1)                | 36,574 (16.6)                | 233,889 (14.5)               |
| 3                        | 7,244 (4.9)                 | 24,951 (11.3)                | 144,098 (8.9)                |
| 4–9                      | 11,813 (8.0)                | 49,497 (22.4)                | 244,315 (15.1)               |
| ≥ 10                     | 2,300 (1.6)                 | 8,915 (4.0)                  | 32,365 (2.0)                 |
| Any other vaccine uptakea| 15,161 (10.3)               | 103,616 (46.9)               | 1,143,377 (70.8)             |

ARS: regional health administration; COVID-19: coronavirus disease; LVT: Lisbon and Tagus Valley; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

a Received at least one of the following vaccines since 2016, influenza vaccine, pneumococcal conjugate vaccines (PCV13, PCV7, or PCV10) and pneumococcal polysaccharide vaccine (PPSV23).
the laboratory-confirmed SARS-CoV-2 infection. We included all death events provided that the laboratory confirmation date occurred during the study period, i.e. even if the death occurred after the study period.

**Exposures definitions**

Data on exposure status were obtained from the population-based electronic vaccination registry (VACINAS). Participants without any registered COVID-19 vaccine dose were classified as *unvaccinated*. Participants were classified as vaccinated with the primary series 14 days following vaccine uptake, according to the product characteristics (single dose of Janssen vaccine or two doses of an mRNA vaccine or Vaxzevria). Only mRNA vaccines were used for the booster doses. Participants were classified as *vaccinated with the first booster* 14 days following the uptake of the mRNA vaccine booster dose. Participants were classified as *vaccinated with the second booster dose* 14 days after the second booster mRNA COVID-19 vaccine dose uptake. Those with documented uptake of any dose of COVID-19 vaccine but who did not fit the above definitions were not included in the study.

For the age group ≥ 80 years, we considered second booster dose uptake as the main exposure and the unvaccinated as the reference group. We also estimated relative vaccine effectiveness (rVE), to quantify the additional protection conferred by the second booster relative to other vaccination regimens.

For the cohorts 60–79 years and ≥ 80 years, we report the VE for the first booster dose and for the primary series during the study period, and rVE to compare protection between first booster dose and primary series.

**Statistical analysis**

Descriptive statistics were used to characterise participants at baseline by exposure level and at the end of the follow-up period. For each outcome and cohort, VE was estimated as $VE = 100\% \times (1 - HR)$, where HR stands for confounder-adjusted hazard ratio obtained through a time-dependent Cox regression model, adjusted for age group (5-year bands), sex, municipality-level European deprivation index quintile [6], number of chronic diseases, number of SARS-CoV-2 laboratory tests during the period 2020 to 2022, previous influenza vaccine or pneumococcal vaccine uptake. Complete case analysis was used.

Data analysis was performed with R software, version 4.0.5 (R Foundation, Vienna, Austria). The statistical significance level was set at 5%.

| Exposure status | Person-years | Events | Rate per 100,000 person-years | VE (95% CI) | rVE second booster and first relative to other vaccination regimens (95% CI) | rVE second booster relative to first booster (95% CI) |
|-----------------|--------------|--------|-------------------------------|-------------|---------------------------------------------------------------------|-------------------------------------------------|
| ≥ 80 year-olds  |              |        |                               |             |                                                                     |                                                  |
| Hospitalisation |              |        |                               |             |                                                                     |                                                  |
| Unvaccinated    | 10,901       | 164    | 1,505                         | Reference   | NA                                                                  | NA                                              |
| Primary series  | 10,491       | 188    | 1,792                         | 56 (46–65)  | Reference                                                           | NA                                              |
| First booster   | 61,637       | 858    | 1,392                         | 63 (55–70)  | 16 (1–28)                                                          | Reference                                         |
| Second booster  | 39,633       | 133    | 336                           | 81 (75–86)  | 53 (43–65)                                                         | 47 (35–57)                                        |
| Death           |              |        |                               |             |                                                                     |                                                  |
| Unvaccinated    | 10,911       | 231    | 2,117                         | Reference   | NA                                                                  | NA                                              |
| Primary series  | 10,503       | 274    | 2,609                         | 58 (49–65)  | Reference                                                           | NA                                              |
| First booster   | 61,702       | 1,209  | 1,959                         | 64 (57–69)  | 13 (1–24)                                                          | Reference                                         |
| Second booster  | 39,646       | 261    | 658                           | 82 (77–85)  | 56 (47–63)                                                         | 49 (41–56)                                        |
| 60–79 year-olds |              |        |                               |             |                                                                     |                                                  |
| Hospitalisation |              |        |                               |             |                                                                     |                                                  |
| Unvaccinated    | 31,482       | 94     | 299                           | Reference   | NA                                                                  | NA                                              |
| Primary series  | 48,566       | 113    | 233                           | 67 (56–75)  | Reference                                                           |                                                  |
| First booster   | 341,824      | 533    | 156                           | 74 (66–80)  | 21 (2–36)                                                          |                                                  |
| Death           |              |        |                               |             |                                                                     |                                                  |
| Unvaccinated    | 31,491       | 67     | 213                           | Reference   | NA                                                                  | NA                                              |
| Primary series  | 48,578       | 120    | 247                           | 59 (44–70)  | Reference                                                           |                                                  |
| First booster   | 341,875      | 523    | 153                           | 65 (54–74)  | 14 (5–10 30)                                                       |                                                  |

COVID-19: coronavirus disease; NA: not applicable; rVE: relative vaccine effectiveness; VE: vaccine effectiveness.
Description of the participants and events
Among 642,067 enrolled Portuguese residents aged ≥80 years, 53.3% received the second booster of a COVID-19 vaccine (Table 1). The coverage with the first booster dose in the age cohort 60–79 years (n= 1,984,107) was 81.4% (Table 2).

Between 15 May 2022 and 31 July 2022, 1,343 COVID-19-related hospitalisations occurred in the ≥80 year-olds and 740 in the 60–79 year-olds, while the number of deaths was 1,975 and 710, respectively.

Vaccine effectiveness against COVID-19-related hospitalisation
In the age cohort ≥ 80 years, the VE against COVID-19-related hospitalisation was 56% (95% CI: 46–65) for the primary vaccine series, 63% (95% CI: 55–70) for the first mRNA booster dose and 81% (95% CI: 75–85) for the second mRNA booster dose (Table 3).

The second booster dose was more effective in preventing COVID-19-related hospitalisations when compared either with the primary series (rVE = 53%; 95% CI: 43–65) or the first booster dose (rVE = 47%; 95% CI: 35–57).

In the age cohort 60–79 years, VE for primary series and the first mRNA booster dose against COVID-19-related hospitalisation was, respectively, 67% (95% CI: 56–75) and 74% (95% CI: 66–80), which represents a rVE of 21% (95% CI: 2–36).

Vaccine effectiveness against COVID-19-related death
For the age cohort ≥ 80 years, we estimated a VE against COVID-19-related death of 58% (95% CI: 50–65) for complete primary vaccination, 64% (95% CI: 57–69) for the first booster dose and 82% (95% CI: 77–85) for the second booster dose.

Uptake of the second mRNA booster dose was associated with a 49% (95% CI: 41–56) reduction in the risk of COVID-19-related death compared with the first booster dose. The protective effects of the first mRNA booster relative to the primary vaccination on preventing COVID-19-related deaths were much lower (rVE = 13%; 95% CI: 1–24).

In the age cohort 60–79 years, we observed a VE of 59% (95% CI: 44–70) and 65% (95% CI: 54–74) for the primary series and the first mRNA booster dose against COVID-19-related death, representing a risk reduction of 14% for COVID-19-related death when comparing first booster dose with the primary vaccine series.

Discussion
Using a cohort of the population 80 years and older, based on electronic health records linkage, we estimated a high VE of the second mRNA booster dose in preventing COVID-19-related hospitalisations (VE = 81%) and deaths (VE = 82%) during the period of BA5 circulation in Portugal. Our estimates are comparable to the one reported for 50-year-olds during the period of Omicron BA.2/BA.2.12.1 predominance in the United States (VE = 80%; 95% CI: 71–85) [7] and residents of long-term care facilities in Canada (VE = 86%; 95% CI: 81–90) [8].

We observed moderate vaccine-induced protection for both primary vaccination and first booster dose in 60–79 year-olds and in those 80 years and older, ranging between 56% and 74% against COVID-19-related hospitalisation and between 58% and 65% against COVID-19-related mortality. Meaning that individuals with primary vaccination or first booster dose maintain an increased protection against COVID-19 severe outcomes compared with unvaccinated individuals.

A significant increase in protection against COVID-19-related hospitalisation and mortality compared with the first booster (rVE = 47% for hospitalisation and rVE = 49% for mortality) are in line with rVE of 42% reported for all-cause mortality in Sweden in the period January to March 2022 for those aged 80 years and older [9]. However, our rVE of the second booster against hospitalisations was lower than reported in Israel for people 60 years and older (74%; 95% CI: 48–91) [10]. Nevertheless, comparisons should be made with caution given the differences in eligible age groups, outcomes and epidemiological context in the countries, mainly the fact that the study period for both these studies was January-February 2022, during early stages of Omicron predominance and our study covers the Omicron BA.5 predominance period in Portugal.

Among the limitations of this study, we should mention the possibility of outcome misclassification bias related to the coding of hospitalisations at discharge. If the vaccination status is associated with shorter length of hospitalisation, the hospitalisations could be more up to date at the time of data extraction in the second booster dose group, and this would bias the VE in the null direction, so we would be underestimating the second booster dose VE. Secondly, there is a possibility of residual confounding in VE estimates, as the number of confounders available in electronic health records is limited, and data on mask use and physical distancing are not available at individual level. Thirdly, although in the establishment of the cohorts we included several steps to reduce the number of duplicates or non-real individuals, we cannot rule out the possibility of non-real individuals in the cohorts. Fourthly, we did not perform genetic characterisation of the viruses. Surveillance data indicated that prevalence of the BA.5 lineage in Portugal during the study period ranged between 64 and 97% [5]. Nevertheless, we cannot assume that all infections were caused by the BA.5 lineage. Thus, we cannot completely generalise our results as VE measurements against the BA.5 Omicron variant. Finally, the follow-up time after the second booster dose was limited, so other studies are needed to address waning of vaccine protection.
Conclusion
For the population aged 80 years and older, our study supports a high VE of the second mRNA booster dose in preventing severe COVID-19-related outcomes, and a relevant increase in protection compared with previous vaccination during Omicron BA.5 predominance. In the group aged 60–79 years, and given that the VE estimates against hospitalisation were lower for the first booster dose compared with early stages of the first booster dose roll-out (74% vs 95%) [11], the recommendation of extending the second booster dose to this age group could have a relevant benefit in terms of COVID-19 impact mitigation.

Ethical statement
The study received approval from the Ethical Committee and the Data Protection Officer of the Instituto Nacional de Saúde Doutor Ricardo Jorge. Given that data was irreversibly anonymised the need for the participants’ informed consent was waived by the Ethical Committee.

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Conflict of interest
None declared.

Authors’ contributions
IK collaborated in the conceptualisation of the study, performed statistical analysis and drafted the first version of the manuscript. BN was involved in the conceptualisation of the study, results interpretation and provided critical comments on the manuscript. SM, RF collaborated in the study design, performed data linkage and critically reviewed the manuscript.

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