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Effectiveness of homologous/heterologous booster COVID-19 vaccination schedules against severe illness in general population and clinical subgroups in three European countries

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ABSTRACT

Using 4 data-sources (Spain, Italy, United Kingdom) data and a 1:1 matched cohort study, we aimed to estimate vaccine effectiveness (VE) in preventing SARS-CoV-2 infections with hospitalisations (±30 days) and death (±56 days) in general population and clinical subgroups with homologous/heterologous booster schedules (Comirnaty-BNT and Spikevax-MOD original COVID-19 vaccines) by comparison with unboosted individuals, during Delta and beginning of Omicron variants. Hazard Ratio (HR, by Cox models) and VE ([1-HR]*100) were calculated by inverse probability weights. Between December 2020-February 2022, in adults without prior SARS-CoV-2 infection, we matched 5.5 million people (>1 million with immunodeficiency, 343,727 with cancer) with a booster (3rd) dose by considering doses 1 and 2 vaccine brands and calendar time, age, sex, region, and comorbidities (immunodeficiency, cancer, severe renal disease, transplant recipient, Down Syndrome). We studied booster doses of BNT and MOD administered after doses 1 and 2 with BNT, MOD, or Oxford-AstraZeneca during a median follow-up between 9 and 16 weeks. BNT or MOD showed VE ranging from 70 to 86% across data sources as heterologous 3rd doses, whereas it was 42–88% as homologous 3rd doses. Depending on the severity and available follow-up, 3rd-dose effectiveness lasted between 1 and 5 months. In people with immunodeficiency and cancer, protection across data sources was detected with both heterologous (VE = 54–83%) and homologous (VE = 49–80%) 3rd doses. Overall, both heterologous and homologous 3rd doses with BTN or MOD showed additional protection against the severe effects of SARS-CoV-2 infections for the general population and for patients at potentially high risk of severe COVID-19 (elderly, people with immunodeficiency and cancer) in comparison with two doses schemes during Delta or early Omicron periods. The early VE after vaccination may be due to less testing among vaccinated pairs and unknown confounders, deserving cautious interpretation. The

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VE wane over time needs further in-depth research to properly envisage when or whether a booster of those vaccines should be administered.

1. Introduction

Since December 2020, eight vaccines (Comirnaty-BNT, Spikevax-MOD, Vaxzevria-AZ, Jcovden, Nuvaxovid, Valneva, VidPrevtyn Beta, and Bimervax) have been progressively approved in Europe to prevent the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1,2]. During the prevalence of the (pre-)Delta variants, people required at least two doses of Comirnaty, Spikevax, and/or Vaxzevria vaccines to be adequately protected (three doses for people with weakened immune systems), whereas, in 13 European countries, population with prior infection were initially considered immunized with a single-dose vaccination [3–5]. Waning of the protection against the Delta variant was observed a few months after the vaccine administration [6] and, booster doses were recommended 3–6 months after the first vaccinations [7]. Then, the Omicron variant became dominant worldwide and led to the highest-ever COVID-19 incidence, also in countries with high vaccination coverage [8–11]. Booster doses have shown effectiveness in providing additional protection to the two doses schemes against severe COVID-19, i.e. related to hospitalizations and/or deaths [12–16]. However, vaccine effectiveness (VE) can vary depending on the vaccine brand or type (e.g., among mRNA or adenoviral platforms) [10]. Mixing brands for the primary vaccinations and/or boosters was widely applied, although the effectiveness of heterologous schedules was limited to immunogenic clinical data [17–20]. EMA fostered heterologous combinations of mRNA and viral vector vaccines as these could produce good levels of SARS-CoV-2 antibodies and higher T-cell responses than homologous vaccinations [7]. COVID-19 VE can also vary among patients boosted with different mRNA vaccines and in relation to the primary vaccinations [11]. Recent real-world evidence studies showed that adenovirus platforms booster with Vaxzevria prevented Omicron COVID-19 infections, offering comparable protection to mRNA vaccines. [21–24]. Additional evidence on the effectiveness of homologous and/or heterologous booster vaccination strategies is needed [11,25–27] to fuel national authorities' and regulators' [20,21] preparedness in case of putative urgent decision-making situations in the future.

In the framework of the "Covid Vaccine Effectiveness" (CoVE) study [27], we assessed in large populations of four EU countries the effectiveness and waning of immunity of homologous and heterologous booster vaccinations with AZD1222 (Vaxzeria; Oxford-AstraZeneca, referred to as AZD), BNT162b2 (Comirnaty; Pfizer-BioNTech, BNT), and mRNA-1273 (Spikevax; Moderna, MOD) through the prevention of hospitalizations and death with COVID-19 in adults (≥18 years old). We could estimate the vaccine effectiveness against hospitalization for Spanish and Italian data sources and, against death, for Spanish and UK data sources.

2. Methods

2.1. Data sources and study design

We report a pan-European retrospective multi-database cohort study that estimated both VE and its duration against hospitalized COVID-19 (in ES-BIFAP, ES-SIDIAP, IT-CASERTA), so-called severe COVID-19 herein, and death with COVID-19 (in ES-BIFAP, ES-SIDIAP and UK-CPRD), which were defined using data source-specific available information (EUPAS 47725). We matched 1:1 adults (≥18 years old) with booster doses (3 doses) vs no booster (2 doses) considering the type of the primary vaccination scheme and the brand of the 1st dose. The study focused on the period ranging from the beginning of the vaccination campaign (December 2020) to the last data available in each data source (ranging from December 2021 to February 2022). Adults with homologous booster doses received the same COVID-19 vaccine brand during the primary vaccination scheme (doses 1 and 2) and a booster dose (dose 3). Heterologous booster doses referred to individuals having received different COVID-19 vaccine brands during the primary vaccination schedules or as a booster dose. Patients with homologous first two doses and a heterologous booster dose were analysed as a separate heterologous booster group from adults that received a heterologous primary vaccination scheme and therefore independently compared to corresponding unboosted individuals (Fig. 1).

We used data from 4 electronic health care databases in Southern, Northern, and Western Europe: the Italian Caserta local health database (IT-CASERTA) [28], the Spanish Pharmacoepidemiological Research Database for Public Health System (ES-BIFAP) [29], the Spanish Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària (ES-SIDIAP) database [30], and the British Clinical Practice Research Datalink (UK-CPRD) Aurum [31]. According to the external and internal data sources comparison, high-quality data on COVID-19 vaccines (i.e., product types and dates), COVID-19 outcomes (i.e., test results, diagnoses in primary and secondary healthcare settings), and covariates of interest were provided and validated by previous EU PE&PV and VAC4EU collaborations (EUPAS 37273, EUPAS 40404, EUPAS 42467) [32,33]. Full details of the conducted COVID-19 VE study are provided in the protocol and report, published online (EUPAS 47725) [27].

2.2. Participants

The study population comprised all adults aged ≥ 18 years registered in any of the data sources during the study period with at least 2 years of available healthcare data prior to the 1st dose vaccination to ensure baseline information. Individuals were defined as boosted (homologous or heterologous) from the date of the 3rd COVID-19 vaccine dose administration, if at least 28 days after the 2nd dose. Participants were defined as unboosted until the date of 3rd vaccine dose administration, thus, potentially selected as control during this period. Boosted participants (3 doses) were matched 1:1 to controls, i.e. unboosted individuals (2 doses only), on the booster date (time 0), based on the brand of the 1st dose, primary vaccination scheme and dates of doses 1 and 2 (±7 days), age, sex, region, and clinical conditions potentially resulting in a high risk of severe COVID-19 (persons with immunodeficiency [including congenital and acquired immunodeficiencies, and those caused by hematological cancers, patients undergoing solid organ transplantation and autoimmune diseases; as well as persons under immunosuppressant [ATC L04] or treatment with immunosuppressant [ATC L04] or systemic corticosteroids [ATC H02]), cancer or malignant tumor, transplants, severe renal disease, and Down syndrome recorded during the two years before the 1st dose). Controls were selected randomly with replacements. Study participants had not encountered SARS-CoV-2 infection prior dose 1.

2.3. Follow-up period and outcome definition

The follow-up period started at time 0 and continued until the earliest occurrence date of severe COVID-19 (defined as hospitalizations with positive SARS-CoV-2 test within 30 days), death, last database data extraction, or moving out from the corresponding data source. A follow-up until death with a recorded positive SARS-CoV-2 test in the previous 56 days (outcome death with COVID-19) was also performed. The follow-ups for both matched subjects were also censored whenever any of them received any extra vaccination dose.

2.4. Statistical analyses

Descriptive characteristics are presented as mean (standard deviation), or overall proportion for each cohort. Incidence rates (IR; 95% confidence intervals (CI)) and IR differences (IRD; 95% CI; controlled by matched criteria) for each COVID-19 outcome were calculated. We used inverse probability weighted (IPW) Cox proportional hazards regression (CI, 95%) to derive the average hazard ratio (HR) of COVID-19-related outcomes. The adjusted VE (%) of boosted vs unboosted cohorts was estimated as 1 minus the adjusted HR multiplied by 100 (corresponding CI calculated as 1–95%). Numerous covariates that are available in each data source (comorbidities, medication use, and health care utilization) and reported listed in Table S1 and report [34] as per protocol [EUPAS47725], have been considered for at least 2 years prior the study period (2018–2020) to measure potential confounders for the IPW. VE for each COVID-19 outcome was estimated by (*i*) vaccine brands and scheme, (*ii*) time after vaccination, (*iii*) 10-by-10 age categories, (*iv*) condition at high risk of severe COVID-19 populations, and (*v*) calendar period of time 0 classified according to the country-specific dominant SARS-CoV-2 variant period (pre-Delta, Delta from 24/05/2021 in the UK or 04/07/2021 in the other countries and Omicrons from 03/01/2022) in accordance with active surveillance data [35,36]. Dominant variants were defined as the variant reaching 50% of the total sequenced specimens. Sensitivity analysis restricting to patients with prior testing for SARS-CoV-2 infection was performed to balance the testing availability among compared people, and control for surveillance bias. Selection of clinical conditions, medication use (including influenza vaccination and others), and primary care physician' visits, based on a potential higher probability to incur COVID-19 (or severe prognosis) and COVID-19 vaccination, and collected up to 2 years before 2020 (see Table S1), were used as potential confounders in the inverse probability weighting (IPW). Random-effects *meta*-analyses using the main estimates from each data source were performed for clinical subgroups per default as an insufficient sample size for individual interpretations was expected [34,37].

3. Results

3.1. Participants

3,127,118 individuals with homologous boosters, mainly received from November 2021 to January 2022, were matched with unboosted pairs. Data were available from all the participant data sources for this cohort. Most of the individuals (2,802,205; 90%) received the BNT vaccine brand (>78% in ES-SIDIAP, ES-BIFAP, IT-CASERTA and UK-CPRD). Mean age ranged from 52 to 75 years old. People with immunodeficiency or having a cancer diagnosis were 544,067 (35% in ES-SIDIAP, 18% in ES-BIFAP, 48% in IT-CASERTA, 4% in UK-CPRD) and 221,933 (17% in ES-SIDIAP, 6% in ES-BIFAP, 8% in IT-CASERTA, 5% in UK-CPRD) pairs across all data sources, respectively, contributing to VE analyses. 2,340,711 individuals with heterologous booster, mainly received in December 2021, after homologous doses 1 and 2, were matched with unboosted individuals. No data were available from the UK data source for this cohort. Most of the patients (1,206,575; 52%)

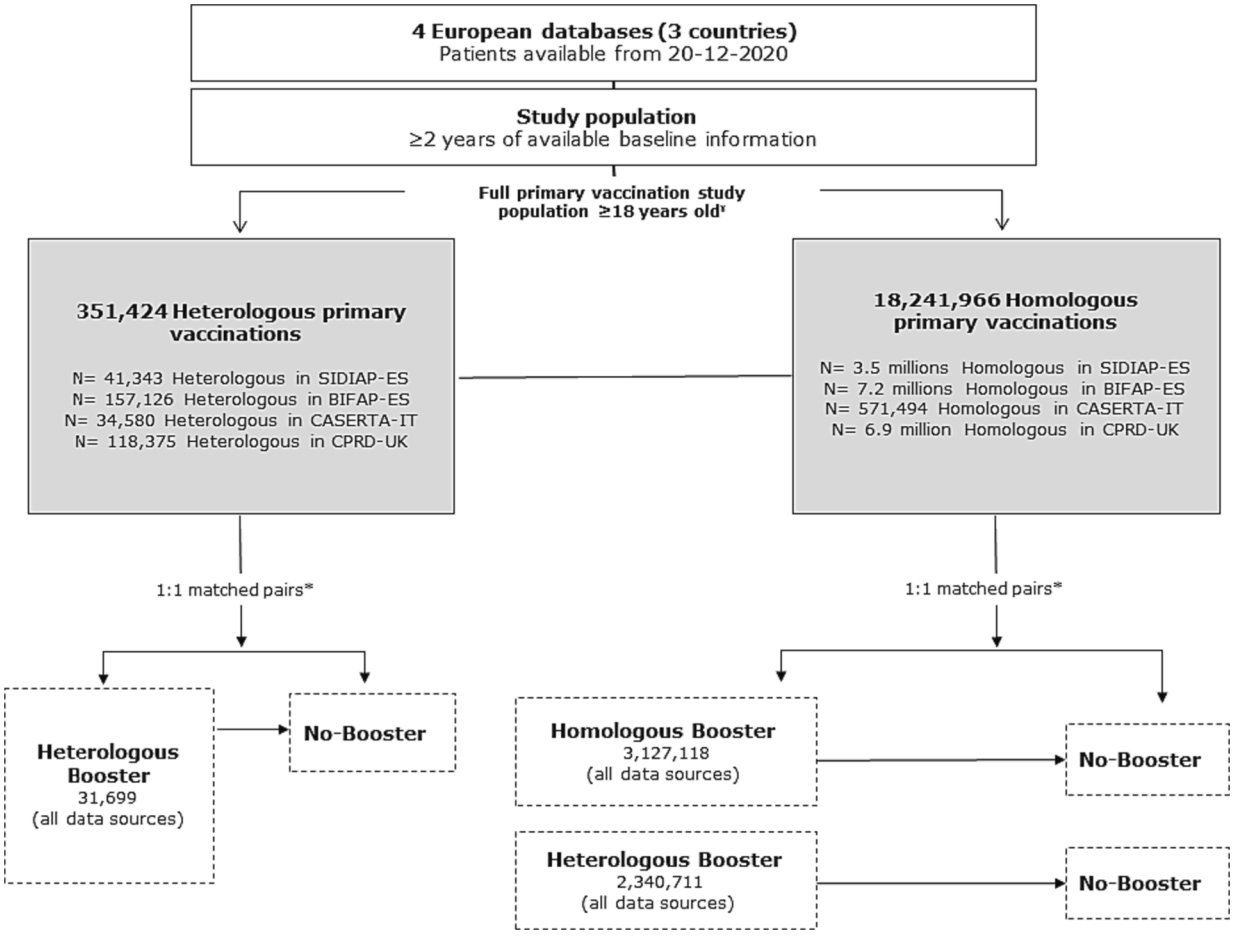

Fig. 1. Study Design. ¥Out of the total of 19 million with full vaccination, 4–6.5% people had encountered SARS-COV-2 infection that were excluded from analysis. *Majority of the people with a booster dose were matched and could participate in the analysis: 91–96% in Spanish and Italian data sources and 55% in the UK data source.

received the BNT vaccine brand during the primary vaccination (48% in ES-BIFAP, 55% in ES-SIDIAP, 60% in IT-CASERTA). The most often administered 3rd doses were MOD (1,974,208; 84% across data sources: 75% in ES-BIFAP, 99% in ES-SIDIAP, 86% in IT-CASERTA). Mean age ranged from 53 to 65 years old, similar to the homologous booster cohort. A total of 31,699 adults with a heterologous booster, mainly received in December 2021, after heterologous doses 1 and 2, were matched with unboosted adults. Data were available from all the data sources. However, VE estimation was not possible due to not enough numbers of cases. The majority of the participants (27,351; 86% across data sources: 99% in ES-SIDIAP, 87% in ES-BIFAP, 100% in IT-CASERTA, 51% in UK-CPRD) received the AZD vaccine as dose 1. The most administered 3rd doses were MOD in Spain (91% in ES-SIDIAP, 59% in ES-BIFAP), and BNT in Italy (94% in IT-CASERTA) and the UK (85% in UK-CPRD). Mean age ranged from 36 to 66 years old, which is lower compared to the other booster cohorts. Descriptive data are shown in Table 1 and S1 by compared groups.

3.2. Booster vaccine effectiveness

Incidence rates (IR; 95% CI) and VE estimations on hospitalization and death with COVID-19 are presented in Tables 2 and 3 overall and by scheme, brand, and variant. VE estimations on waning of immunity, age, and clinical subgroups are shown in Table 4, Table 5 and Tables S2-S5. IR differences are reported in text for people aged > 80 years. VE estimations are available only for different 3-doses schemes with homologous doses 1 and 2.

3.3. Booster vaccine effectiveness against hospitalization with COVID-19

We observed 1,015 cases of hospitalization with COVID-19 in boosted adults whereas 3,362 episodes were encountered among the unboosted comparators. All these cases received a homologous primary vaccination. The majority of cases were in people ≥ 60 years old (87%) from ES-BIFAP or ES-SIDIAP, and only a few in IT-CASERTA. In particular, for the > 80 years old individuals with homologous booster doses, the IRD of hospitalization with COVID-19 was −4.25 (95% CI: −4.77 to −3.74) for BIFAP, −3.63 (95% CI: −4.59 to −2.68) for SIDIAP, and −0.20 (95% CI: −0.49 to 0.08) for CASERTA. For heterologous boosters, IRD was −6.30 (95% CI: −7.67 to −4.92) for BIFAP, and −5.69 (95% CI: −7.41 to −3.97) for SIDIAP. In immunocompromised patients, the IRD was −3.39 (95% CI: −3.98 to −2.79) for BIFAP, −3.44 (95% CI: −4.46 to −2.42) for SIDIAP, and −0.28 (95% CI: −0.53 to −0.04) for CASERTA for homologous boosters, whereas, for those with heterologous boosters, IRD was −3.20 (95% CI: −3.73 to −2.66) for BIFAP, −4.23 (95% CI: −5.31 to −3.16) for SIDIAP, and −0.05 (95% CI: −0.16 to 0.05) for CASERTA.

In CASERTA, the adjusted VE was 80% (95% CI: 10–96%) for people receiving a homologous booster dose. Other stratified analyses could not be performed for this data source due to insufficient cases. The adjusted VE was then calculated for the Spanish data sources. For the homologous booster doses, VE was 67% (95% CI: 64–70%) and 61% (95% CI: 53–68%), whereas a VE of 75% (95% CI: 71–78%) and 79% (95% CI: 73–83%) for heterologous booster doses was observed in BIFAP and SIDIAP, respectively. To ease the reading, some confidence intervals are reported only in Table 2. Hereafter, we report the ranges of VE across data sources or vaccine brands. Unless specified, all VEs were statistically significant. Considering the vaccine brand, for adults having received BNT as homologous 3 doses, VE was 64–67%. For booster doses of MOD after BNT dose 1 and 2, the VE was 74–78%. Adults with homologous 3 MOD doses had a VE of 42–65%. For booster doses of BNT after MOD doses 1 and 2, the VE was 73–78%. Homologous AZD doses 1 and 2 followed by BNT or MOD as booster resulted in a VE of 76% (95% CI: 69–81%)-81% (95% CI: 69–89%). No sufficient data was available for VE estimation of AZD booster doses.

Considering the VE against different SARS-CoV-2 variants, in ES-BIFAP, VE of homologous 3 doses was similar for the Delta and Omicron periods, 68% (95% CI: 63–72%) and 67% (95% CI: 62–71%), respectively. The same is observed for heterologous boosters, 77% (95% CI: 71–82%) and 74% (95% CI: 69–78%), respectively. In ES-SIDIAP, the follow-up time only covered the Delta period, and VE was 61% (95% CI: 53–68%) for homologous boosters and 79% (95% CI: 73–83%) for heterologous ones. Protection against hospitalization with COVID-19 from homologous or heterologous boosters was observed whenever enough cases occurred, mainly among ≥ 50 and ≥ 70 years old in ES-BIFAP and ES-SIDIAP, respectively. For both schemes, a VE decrement was observed with age (Table S2). For instance, for heterologous booster VE, from 50 to 59 years old (90% in ES-SIDIAP; 73% in ES-BIFAP) to ≥ 80 years old (67% in ES-SIDIAP; 66% in ES-BIFAP) adults, with an intermediate increment from 50 to 79 years old in ES-BIFAP (Table S2). A significant VE was observed from the first week after the 3rd vaccination whether homologous or heterologous. In Spain, homologous boosters' VE remained significant for 2 and 5 months (Table 4), whereas, for heterologous boosters, the significant VE duration was shorter (1 and 3 months) (Table 4). Performing sensitivity analyses by restricting to adults having tested for SARS-CoV-2 before matching in the two Spanish data sources, the VE values remained significant, with a decrease for the homologous booster [i.e., 55% (95% CI: 40–66%) and 59% (95% CI: 52–66%)], and a slight changes [81% (95% CI: 73–87%) and 70% (95% CI: 62–77%)] for the heterologous one.

3.4. Booster vaccine effectiveness against death with COVID-19

We observed 313 cases of death with SARS-CoV-2 infection in boosted adults whereas 1,367 events were encountered among the unboosted comparators, mostly in ES-BIFAP and ES-SIDIAP and a few in UK-CPRD. Most cases occurred in people ≥ 60 years old (97%). All reported deaths with COVID-19 occurred in the homologous primary vaccination cohort, and most of them received a homologous booster dose.

The IRD of death with COVID-19 among > 80 years old individuals with homologous booster doses was −2.82 (95% CI: −3.21 to −2.43) for BIFAP, −2.56 (95% CI: −3.21 to −1.90) for SIDIAP and −0.40 (95% CI: −0.64 to −0.15) for CPRD. For heterologous boosters, IRD was −7.14 (95% CI: −8.37 to −5.90) for BIFAP and −4.09 (95% CI: 5.31 to −2.87) for SIDIAP. In immunocompromised adults, the IRD was −1.66 (95% CI: −2.04 to −1.28) for BIFAP, −1.96 (95% CI: −2.57 to −1.35) for SIDIAP and 0.00 (95% CI: −0.52 to 0.52) for CPRD for homologous boosters, whereas, for heterologous boosters, IRD was −1.33 (95% CI: −1.65 to −1.02) for BIFAP and −1.16 (95% CI: −1.70 to −0.62) for SIDIAP.

In this cohort, independently of the vaccine brands, the VE against death ranged, across data sources, from 74 to 80% for homologous boosters and 82–86% for heterologous booster ones, compared to unboosted pairs. VE of homologous BNT 3 doses ranged 72–79% across data sources. MOD homologous 3 doses were only available for ES-BIFAP, with a VE of 88% (95% CI: 74–95%). These values referred only to > 60 years old. No sufficient data was available for AZD booster doses. Regardless of doses 1 and 2 brands, a MOD booster showed a VE of 83–86% in Spain, whereas a BNT booster dose showed (only for ES-BIFAP) a VE of 77%, compared to unboosted controls. There were not enough events (<5) for the AZD booster. During the Delta period, VE of homologous 3 doses was 76–80% across three data sources (ES-BIFAP, ES-SIDIAP, UK-CPRD), whereas was 80–86% for heterologous booster in Spain. During the Omicron period, only data from ES-BIFAP was available, with a VE of 72% and 83% for homologous and heterologous booster doses, respectively. A statistically significant VE started the first week after the 3rd dose across data sources. Then, in ES-BIFAP, VE seemed to last for 5 and 4 months after homologous and heterologous 3rd doses, respectively. The other data sources had a shorter follow-up period, with a waning of immunity after 2 months and 2 weeks for homologous and heterologous boosters, respectively, in ES-SIDIAP. Following sensitivity analyses (restricting to adults having tested for

Table 1
Distribution of the matching criteria, 3rd dose vaccine brand, and follow-up time (days) of the boosted individuals who were matched to unboosted pairs for the effectiveness analysis, by vaccination schedule.

Data source	BIFAP-ES			SIDIAP-ES			CASERTA-IT			CPRD-UK	
Booster Schedule*	**HOp_HOb**	**HOp_HEb**	**HEp_HEb**	**HOp_HOb**	**HOp_HEb**	**HEp_HEb**	**HOp_HOb**	**HOp_HEb**	**HEp_HEb**	**HOp_HOb**	**HEp_HEb**
Boosted participants	1,522,416	1,303,411	5,801	356,790	850,525	3,414	218,106	186,775	15,236	1,029,806	7,248
1st dose brand											
AZD	130 (<0.1%)	630,730 (48%)	5,022 (87%)	26 (<0.1%)	377,908 (44%)	3,383 (99%)	–	72,207 (39%)	15,236 (100%)	4,393 (0.4%)	3,710 (51%)
MOD	197,976 (13%)	49,313 (3.8%)	218 (3.8%)	78,708 (22%)	2,026 (0.2%)	<5	43,466 (20%)	1,952 (1.0%)	–	214 (<0.1%)	7 (<0.1%)
BNT	1,324,310 (87%)	623,368 (48%)	561 (9.7%)	278,056 (78%)	470,591 (55%)	27 (0.8%)	174,640 (80%)	112,616 (60%)	–	1,025,199 (100%)	3,531 (49%)
3rd dose brand											
AZD	130 (<0.1%)	30 (<0.1%)	13 (0.2%)	26 (<0.1%)	18 (<0.1%)	<5	–	–	–	4,393 (0.4%)	526 (7.3%)
MOD	197,976 (13%)	974,360 (75%)	3,421 (59%)	78,708 (22%)	838,957 (99%)	3,108 (91%)	43,466 (20%)	160,891 (86%)	989 (6.5%)	214 (<0.1%)	555 (7.7%)
BNT	1,324,310 (87%)	329,021 (25%)	2,367 (41%)	278,056 (78%)	11,550 (1.4%)	304 (8.9%)	174,640 (80%)	25,884 (14%)	14,247 (94%)	1,025,199 (100%)	6,167 (85%)
Charactersitcs											
Female	890,950 (59%)	718,501 (55%)	3,619 (62%)	206,308 (58%)	472,804 (56%)	2,090 (61%)	113,911 (52%)	98,891 (53%)	7,374 (48%)	598,210 (58%)	4,107 (57%)
Mean Age (SD)	72.1 (14.9)	59.3 (13.5)	50.3 (13.8)	74.6 (14.7)	64.6 (13.4)	46.6 (10.9)	52.2 (20.8)	53.5 (13.9)	36.3 (13.0)	65.4 (16.2)	66.1 (15.7)
Immuno-deficiency	274,354 (18%)	218,580 (17%)	789 (14%)	123,193 (35%)	208,170 (24%)	583 (17%)	105,715 (48%)	91,686 (49%)	5,928 (39%)	40,805 (4.0%)	76 (1.0%)
Cancer	93,165 (6.1%)	38,363 (2.9%)	74 (1.3%)	59,946 (17%)	74,656 (8.8%)	105 (3.1%)	18,190 (8.3%)	8,302 (4.4%)	153 (1.0%)	50,632 (4.9%)	141 (1.9%)
Transplant recipient	3,038 (0.2%)	261 (<0.1%)	<5	4,129 (1.2%)	575 (<0.1%)	<5	–	–	–	–	–
Severe renal disease	11,734 (0.8%)	1,562 (0.1%)	<5	4,698 (1.3%)	1,377 (0.2%)	<5	612 (0.3%)	46 (<0.1%)	<5	813 (<0.1%)	<5
Down syndrome	216 (<0.1%)	37 (<0.1%)	<5	175 (<0.1%)	136 (<0.1%)	<5	63 (<0.1%)	5 (<0.1%)	<5	–	–
*FU** (days)*											
Mean (SD)	27.5 (38.7)	28.7 (42.5)	36.3 (49.5)	22.1 (20.3)	9.8 (8.9)	10.0 (11.5)	23.9 (25.2)	18.8 (18.5)	14.8 (15.1)	17.7 (16.8)	19.1 (24.9)
Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
25%	5.0	4.0	4.0	7.0	3.0	3.0	4.0	3.0	3.0	5.0	5.0
Median	13.0	10.0	11.0	16.0	8.0	9.0	16.0	14.0	9.0	12.0	11.0
75%	31.0	24.0	43.0	33.0	14.0	14.0	35.0	27.0	23.0	25.0	24.0
Maximum	339.0	292.0	324.0	234.0	212.0	173.0	144.0	144.0	140.0	239.0	208.0

CASERTA: the Italian Caserta local health database; BIFAP: the Spanish Pharmacoepidemiological Research Database for Public Health System; SIDIAP: the Spanish Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària database; CPRD: the British Clinical Practice Research Datalink Aurum. *HOp = Homologous primary vaccination Schedule; HEp = Heterologous primary vaccination schedule; HOb = Homologous booster dose; Heb = Heterologous booster dose; **FU = follow up time (days); All the table details are referring to the matching date. Data reporting on less than 5 participants is not presented for privacy reasons.

Table 2
Hospitalization with COVID-19 vaccine effectiveness (VE) values.

	Data source	Control person-days	Control cases	Control IR/ 100,000	Exposed person-days	Exposed cases	Exposed IR/ 100,000	HR adjusted	LCI	UCI	VE adjusted	LCI	UCI
HOp_HOb													
Overall	BIFAP	43269303	1547	3.58	43352456	528	1.22	0.33	0.30	0.36	67%	64%	70%
Overall	SIDIAP	8228666	364	4.42	8235337	145	1.76	0.39	0.32	0.47	61%	53%	68%
Overall	CASERTA	5444106	11	0.20	5444298	<5	0.04	0.20	0.04	0.90	80%	10%	96%
BNT	BIFAP	36172189	1403	3.88	36247190	476	1.31	0.33	0.29	0.36	67%	64%	71%
BNT	SIDIAP	6434452	314	4.88	6440421	118	1.83	0.36	0.29	0.45	64%	55%	71%
BNT	CASERTA	4339345	<5	0.09	4339429	<5	0.05	0.57	0.10	3.09	43%	−209%	90%
MOD	BIFAP	7087035	144	2.03	7095187	52	0.73	0.35	0.26	0.49	65%	51%	74%
MOD	SIDIAP	1791767	50	2.79	1792469	27	1.51	0.58	0.36	0.94	42%	6%	64%
Sensit. Negative test	BIFAP	11063469	455	4.11	11087325	192	1.73	0.41	0.34	0.48	59%	52%	66%
Sensit. Negative test	SIDIAP	2643117	152	5.75	2645924	69	2.61	0.45	0.34	0.60	55%	40%	66%
Delta	BIFAP	26209211	831	3.17	26222885	276	1.05	0.32	0.28	0.37	68%	63%	72%
Delta	SIDIAP	8227633	364	4.42	8234304	145	1.76	0.39	0.32	0.47	61%	53%	68%
Delta	CASERTA	3102789	<5	0.10	3102792	<5	0.03	0.37	0.04	3.60	63%	−260%	96%
Omicron	BIFAP	17184114	734	4.27	17221221	256	1.49	0.33	0.29	0.38	67%	62%	71%
Omicron	CASERTA	2399442	10	0.42	2399592	<5	0.08	0.22	0.05	1.00	78%	0%	95%
HOp_HEb													
Overall	BIFAP	38599538	1039	2.69	38665590	257	0.66	0.25	0.22	0.29	75%	71%	78%
Overall	SIDIAP	9187155	401	4.36	9192687	85	0.92	0.21	0.17	0.27	79%	73%	83%
1st dose BNT	BIFAP	22669955	609	2.69	22705586	153	0.67	0.26	0.22	0.31	74%	69%	78%
1st dose BNT	SIDIAP	5640873	297	5.27	5645155	65	1.15	0.22	0.17	0.29	78%	71%	83%
1st dose MOD	BIFAP	1850896	57	3.08	1854298	12	0.65	0.22	0.12	0.41	78%	59%	88%
1st dose MOD	SIDIAP	42291	<5	7.09	42363	<5	2.36	0.27	0.03	2.63	73%	−163%	97%
1st dose AZD	BIFAP	14078687	373	2.65	14105706	92	0.65	0.24	0.19	0.31	76%	69%	81%
1st dose AZD	SIDIAP	3503991	101	2.88	3505169	19	0.54	0.19	0.11	0.31	81%	69%	89%
3th dose BNT	BIFAP	8159498	247	3.03	8177489	59	0.72	0.24	0.18	0.32	76%	68%	82%
3th dose BNT	SIDIAP	192119	5	2.60	192193	<5	1.04	0.35	0.07	1.82	65%	−82%	93%
3th dose MOD	BIFAP	30437969	792	2.60	30486030	198	0.65	0.25	0.22	0.30	75%	70%	78%
3th dose MOD	SIDIAP	8994410	396	4.40	8999868	83	0.92	0.21	0.17	0.27	79%	73%	83%
Sensit. Negative test	BIFAP	9065585	273	3.01	9082301	80	0.88	0.30	0.23	0.38	70%	62%	77%
Sensit. Negative test	SIDIAP	2934634	169	5.76	2936947	32	1.09	0.19	0.13	0.27	81%	73%	87%
Delta	BIFAP	13009885	370	2.84	13014173	84	0.65	0.23	0.18	0.29	77%	71%	82%
Delta	SIDIAP	9186801	401	4.36	9192333	85	0.92	0.21	0.17	0.27	79%	73%	83%
Omicron	BIFAP	25748291	675	2.62	25790669	175	0.68	0.26	0.22	0.31	74%	69%	78%

CASERTA: the Italian Caserta local health database; BIFAP: the Spanish Pharmacoepidemiological Research Database for Public Health System; SIDIAP: the Spanish Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària database; CPRD: the British Clinical Practice Research Datalink Aurum. HOp = Homologous primary vaccination Schedule; HEp = Heterologous primary vaccination schedule; HOb = Homologous booster dose; Heb = Heterologous booster dose; Control group = Non boosted adults; Exposed group = boosted adults; VE = Vaccine effectiveness; HR = Hazard ratio; IR = Incidence rates; adj. = Adjusted. PreDelta period was removed from tables due to less than 5 cases and so limitation to estimate incidence rates above 0.00 per 100,000 person-days. The categories in which VE could not be estimated due to lack of sample size or number of cases are not reported in the table. Consequently, the number of person-days and cases do not sum up to the overall identified. Data reporting on less than 5 participants is not presented for privacy reasons.

COVID-19 before matching), in Spain, VEs remained statistically significant: 67–79% for the homologous cohort, and 77–81% for the heterologous one.

3.5. Booster vaccine effectiveness for clinical subgroups

Pooled VE (3vs2 doses) from *meta*-analysis is shown in Fig. 2 and discussed here. In immunocompromised adults, the VE against hospitalization of homologous 3 doses was 62% (pooled VE; 95% CI: 57–67%; $I^2 = 0\%$) in Spain and 78% (95% CI: 0–95%) in Italy, while 72% (95% CI: 66 to 77%; $I^2 = 0\%$) with heterologous booster. For death with COVID-19, in Spain, pooled VE was 73% (95% CI: 63–80%; $I^2 = 15\%$) for homologous 3 doses and 80% (95% CI: 70–86%; $I^2 = 0\%$) for heterologous boosters.

In adults with cancer or malignant tumor, in Spain, the pooled VE of homologous 3 doses against hospitalization was 54% (95% CI: 41–64%; $I^2 = 18\%$) while, for heterologous boosters, was 68% (95% CI: 36–84%; $I^2 = 77\%$). Pooled VE against death with COVID-19 across Spanish data sources was 75% (95% CI: 65–82%; $I^2 = 0\%$) for homologous 3 doses and 81% (95% CI: 70–89%; $I^2 = 0\%$) for heterologous boosters. There

Table 3
Death with COVID-19 vaccine effectiveness (VE) values.

	Data source	Control person-days	Control cases	Control IR/ 100,000	Exposed person-days	Exposed cases	Exposed IR/100,000	HR adjusted	LCI	UCI	VE adjusted	LCI	UCI
HOp_HOb													
Overall	BIFAP	43361621	675	1.56	43371503	189	0.44	0.26	0.22	0.31	74%	69%	78%
Overall	SIDIAP	8235852	156	1.89	8237787	33	0.40	0.20	0.14	0.30	80%	70%	86%
Overall	CPRD	19245486	26	0.14	19245639	6	0.03	0.23	0.10	0.57	77%	43%	90%
BNT	BIFAP	36254930	622	1.72	36264044	182	0.50	0.28	0.23	0.33	72%	67%	77%
BNT	SIDIAP	6440559	149	2.31	6442344	33	0.51	0.21	0.14	0.30	79%	70%	86%
BNT	CPRD	19085685	25	0.13	19085838	6	0.03	0.24	0.10	0.59	76%	41%	90%
MOD	BIFAP	7096612	53	0.75	7097380	7	0.10	0.12	0.05	0.26	88%	74%	95%
Sensit. Negative test	BIFAP	11091510	209	1.88	11094570	72	0.65	0.33	0.25	0.44	67%	56%	75%
Sensit. Negative test	SIDIAP	2646002	73	2.76	2646840	16	0.60	0.21	0.12	0.36	79%	64%	88%
Delta	BIFAP	26221304	346	1.32	26225972	87	0.33	0.24	0.19	0.31	76%	69%	81%
Delta	SIDIAP	8234819	156	1.89	8236754	33	0.40	0.20	0.14	0.30	80%	70%	86%
Delta	CPRD	19234897	26	0.14	19235050	6	0.03	0.23	0.10	0.57	77%	43%	90%
Omicron	BIFAP	17270857	338	1.96	17274842	104	0.60	0.28	0.23	0.35	72%	65%	77%
HOp_HEb													
Overall	BIFAP	38670418	390	1.01	38676283	70	0.18	0.18	0.14	0.23	82%	77%	86%
Overall	SIDIAP	9192245	120	1.31	9193354	15	0.16	0.14	0.08	0.23	86%	77%	92%
1st dose BNT	BIFAP	22707084	305	1.34	22711989	52	0.23	0.17	0.13	0.23	83%	77%	87%
1st dose BNT	SIDIAP	5644657	112	1.98	5645665	14	0.25	0.13	0.08	0.24	87%	76%	92%
1st dose MOD	BIFAP	1854938	18	0.97	1855021	5	0.27	0.30	0.11	0.80	70%	20%	89%
1st dose AZD	BIFAP	14108396	67	0.47	14109273	13	0.09	0.20	0.11	0.37	80%	63%	89%
1st dose AZD	SIDIAP	3505217	8	0.23	3505318	<5	0.03	0.14	0.02	1.15	86%	−15%	98%
3th dose BNT	BIFAP	8179299	60	0.73	8179799	13	0.16	0.23	0.12	0.41	77%	59%	88%
3th dose MOD	BIFAP	30489048	330	1.08	30494413	57	0.19	0.17	0.13	0.23	83%	77%	87%
3th dose MOD	SIDIAP	8999394	119	1.32	9000489	15	0.17	0.14	0.08	0.23	86%	77%	92%
Sensit. Negative test	BIFAP	9084028	119	1.31	9085721	22	0.24	0.19	0.12	0.30	81%	70%	88%
Sensit. Negative test	SIDIAP	2936755	44	1.50	2937138	9	0.31	0.23	0.11	0.47	77%	53%	89%
Delta	BIFAP	13013634	115	0.88	13014793	22	0.17	0.20	0.13	0.32	80%	68%	87%
Delta	SIDIAP	9191891	120	1.31	9193000	15	0.16	0.14	0.08	0.23	86%	77%	92%
Omicron	BIFAP	25816888	280	1.08	25821020	48	0.19	0.17	0.13	0.23	83%	77%	87%

CASERTA: the Italian Caserta local health database; BIFAP: the Spanish Pharmacoepidemiological Research Database for Public Health System; SIDIAP: the Spanish Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària database; CPRD: the British Clinical Practice Research Datalink Aurum. HOp = Homologous primary vaccination Schedule; HEp = Heterologous primary vaccination schedule; HOb = Homologous booster dose; Heb = Heterologous booster dose; Control group = Non boosted adults; Exposed group = boosted adults; VE = Vaccine effectiveness; HR = Hazard ratio; IR = Incidence rates; adj. = Adjusted. PreDelta period was removed from tables due to <5 cases and so limitation to estimate incidence rates above 0.00 per 100,000 person-days. The categories in which VE could not be estimated due to lack of sample size or number of cases are not reported in the table. Consequently, the number of person-days and cases do not sum up to the overall identified. Data reporting on less than 5 participants is not presented for privacy reasons.

were no (or less than 5) reported cases in UK-CPRD.

The pooled VE of homologous 3 doses against hospitalization was 24% (95% CI: −54–63%; $I^2 = 0\%$) for patients with a transplant, and 57% (95% CI: −20–84%; $I^2 = 65\%$) for patients with severe renal disease. VE of 75% (95% CI: −38–96%; $I^2 = 63\%$) against COVID-19 with death was observed for people with severe renal disease and homologous 3 doses. Spanish data sources contributed to all estimators (weight of ES-BIFAP and ES-SIDIAP was > 95%), while IT-CASERTA (weight ≤ 1.64%) and UK-CPRD (weight ≤ 2.5%) only to hospitalization and death with COVID-19, respectively.

4. Discussion

Homologous and heterologous 3rd doses with mRNA vaccines, administrated at least 28 days from the 2nd dose, provided additional protection against both hospitalization with COVID-19 (according to two Spanish and Italian data sources) and death with COVID-19 (according to Spanish and UK data sources). This has been observed during the Delta and initial stage of Omicron variant periods (as showed in RCT [38]), with less than 6 months duration. The benefit of booster vaccination was also observed for > 60 years old people, although the VE was lower in ≥ 80 years old. In accordance with clinical trial studies [19] and public health recommendations [7] about switching to mRNA boosters after AZ, the booster VE was also observed for these vaccinees. The booster VE absolute impact, crucial for benefit-risk assessment, resulted highest among the oldest individuals, reducing 4 hospitalizations and 3 deaths with COVID-19 per 100,000 person-days in > 80 years old individuals with homologous doses, whereas, for heterologous booster, reduced 6 hospitalizations and 4–7 deaths with COVID-19 per 100,000 person-days. In Spain, this effectiveness was confirmed independently of

Table 4
Hospitalization with COVID-19: waning of immunity.

	Data source	Control person-days	Control cases	Control IR/ 100,000	Exposed person-days	Exposed cases	Exposed IR/ 100,000	HR adjusted	LCI	UCI	VE adjusted	LCI	UCI
HOp_HOb													
0–6 days	BIFAP	8983642	211	2.35	8984067	106	1.18	0.48	0.38	0.61	52%	39%	62%
0–6 days	SIDIAP	2209918	61	2.76	2210004	45	2.04	0.70	0.47	1.04	30%	−4%	53%
7–13 days	BIFAP	6136241	175	2.85	6136620	55	0.90	0.30	0.22	0.41	70%	59%	78%
7–13 days	SIDIAP	1642068	69	4.20	1642194	23	1.40	0.34	0.21	0.54	66%	46%	79%
14–29 days	BIFAP	8428650	322	3.82	8430648	63	0.75	0.19	0.15	0.25	81%	75%	85%
14–29 days	SIDIAP	2320294	119	5.13	2320945	34	1.46	0.28	0.19	0.41	72%	59%	81%
14–29 days	CASERTA	1425198	<5	0.14	1425198	<5	0.07	0.56	0.05	6.20	44%	−520%	95%
2nd month (30–59 days)	BIFAP	7511606	427	5.68	7516498	90	1.20	0.21	0.16	0.26	79%	74%	84%
2nd month (30–59 days)	SIDIAP	1608082	92	5.72	1609070	28	1.74	0.30	0.19	0.46	70%	54%	81%
3rd month (60–89 days)	BIFAP	4118235	209	5.07	4121083	59	1.43	0.27	0.21	0.37	73%	63%	79%
3rd month (60–89 days)	SIDIAP	310389	19	6.12	310478	12	3.87	0.61	0.29	1.29	39%	−29%	71%
3rd month (60–89 days)	CASERTA	345654	<5	0.29	345668	<5	0.29	1.17	0.07	18.66	−17%	−1 766%	93%
4th month (90–120 days)	BIFAP	2902910	84	2.89	2903499	62	2.14	0.67	0.49	0.93	33%	7%	51%
4th month (90–120 days)	SIDIAP	29532	<5	3.39	29528	<5	3.39	0.83	0.05	13.25	17%	−1 225%	95%
5th month (121–150 days)	BIFAP	1579884	67	4.24	1580260	37	2.34	0.49	0.33	0.74	51%	26%	67%
6th month (151–180 days)	BIFAP	355161	26	7.32	355288	22	6.19	0.74	0.42	1.31	26%	−31%	58%
7th month (181–210 days)	BIFAP	41310	<5	4.84	41286	<5	7.27	1.59	0.26	9.86	−59%	−886%	74%
HOp_HEb													
0–6 days	BIFAP	7356298	222	3.02	7356863	75	1.02	0.34	0.26	0.44	66%	56%	74%
0–6 days	SIDIAP	4655076	175	3.76	4655543	54	1.16	0.30	0.22	0.41	70%	59%	78%
7–13 days	BIFAP	4524649	132	2.92	4524933	42	0.93	0.33	0.23	0.46	67%	54%	77%
7–13 days	SIDIAP	2430909	123	5.06	2431231	19	0.78	0.16	0.10	0.25	84%	75%	90%
14–29 days	BIFAP	5511043	209	3.79	5512356	15	0.27	0.07	0.04	0.12	93%	88%	96%
14–29 days	SIDIAP	1646994	92	5.59	1647752	10	0.61	0.11	0.06	0.22	89%	78%	94%
2nd month (30–59 days)	BIFAP	6317412	261	4.13	6320418	37	0.59	0.14	0.10	0.20	86%	80%	90%
3rd month (60–89 days)	BIFAP	5251802	142	2.70	5253677	39	0.74	0.29	0.20	0.41	71%	59%	80%
4th month (90–120 days)	BIFAP	3358118	28	0.83	3358145	17	0.51	0.65	0.36	1.20	35%	−20%	64%
5th month (121–150 days)	BIFAP	1110571	17	1.53	1110598	15	1.35	0.97	0.48	1.96	3%	−96%	52%
6th month (151–180 days)	BIFAP	156893	<5	0.64	156858	<5	1.28	2.34	0.21	25.84	−134%	−2 484%	79%

CASERTA: the Italian Caserta local health database; BIFAP: the Spanish Pharmacoepidemiological Research Database for Public Health System; SIDIAP: the Spanish Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària database; CPRD: the British Clinical Practice Research Datalink Aurum. HOp = Homologous primary vaccination Schedule; HEp = Heterologous primary vaccination schedule; HOb = Homologous booster dose; Heb = Heterologous booster dose; Control group = Non boosted adults; Exposed group = boosted adults; VE = Vaccine effectiveness; HR = Hazard ratio; IR = Incidence rates; adj. = Adjusted. The categories in which VE could not be estimated due to lack of sample size or number of cases are not reported in the table. Consequently, the number of person-days and cases do not sum up to the overall identified. Data reporting on less than 5 participants is not presented for privacy reasons.

the COVID-19 testing frequency and so controlled by unmeasured confounders.

Considering people with immunodeficiency (identified with their medical condition or drug proxies) and cancer, independently of the vaccine brands, our meta-analyses showed (with low or no heterogeneity) that booster doses conferred also additional protection against both hospitalization and death with COVID-19, especially the latter [39]. People with severe renal disease benefitted from a homologous 3rd

Table 5
Death with COVID-19: waning of immunity.

	Data source	Control person-days	Control cases	Control IR/ 100,000	Exposed person-days	Exposed cases	Exposed IR/ 100,000	HR adjusted	LCI	UCI	VE adjusted	LCI	UCI
HOp_HOb													
0–6 days	BIFAP	8984074	71	0.79	8984229	26	0.29	0.36	0.23	0.56	64%	44%	77%
0–6 days	SIDIAP	2210046	20	0.90	2210092	7	0.32	0.33	0.14	0.78	67%	22%	86%
0–6 days	CPRD	6174302	10	0.16	6174317	<5	0.03	0.20	0.04	0.91	80%	9%	96%
7–13 days	BIFAP	6136600	67	1.09	6136744	15	0.24	0.22	0.13	0.39	78%	61%	87%
7–13 days	SIDIAP	1642198	28	1.71	1642262	5	0.30	0.16	0.06	0.41	84%	59%	94%
7–13 days	CPRD	4203975	<5	0.10	4203984	<5	0.02	0.26	0.03	2.29	74%	−129%	97%
14–29 days	BIFAP	8430134	129	1.53	8430937	22	0.26	0.16	0.10	0.26	84%	74%	90%
14–29 days	SIDIAP	2320801	52	2.24	2321101	10	0.43	0.20	0.10	0.40	80%	60%	90%
14–29 days	CPRD	5331980	8	0.15	5332011	<5	0.04	0.26	0.05	1.21	74%	−21%	95%
2nd month (30–59 days)	BIFAP	7515236	205	2.73	7517076	42	0.56	0.19	0.14	0.27	81%	73%	86%
2nd month (30–59 days)	SIDIAP	1608912	51	3.17	1609365	6	0.37	0.11	0.05	0.25	89%	75%	95%
2nd month (30–59 days)	CPRD	3117616	<5	0.13	3117634	<5	0.03	0.25	0.03	2.21	75%	−121%	97%
3rd month (60–89 days)	BIFAP	4120037	144	3.50	4121344	37	0.90	0.24	0.17	0.35	76%	65%	83%
3rd month (60–89 days)	SIDIAP	310552	5	1.61	310582	<5	0.97	0.51	0.12	2.16	49%	−116%	88%
4th month (90–120 days)	BIFAP	2903943	34	1.17	2903936	32	1.10	0.86	0.53	1.39	14%	−39%	47%
5th month (121–150 days)	BIFAP	1580424	16	1.01	1580587	5	0.32	0.25	0.09	0.70	75%	30%	91%
HOp_HEb													
0–6 days	BIFAP	7356907	32	0.43	7356983	12	0.16	0.38	0.20	0.74	62%	26%	80%
0–6 days	SIDIAP	4655495	42	0.90	4655623	10	0.21	0.25	0.12	0.50	75%	50%	88%
7–13 days	BIFAP	4525002	34	0.75	4525060	8	0.18	0.26	0.12	0.55	74%	45%	88%
7–13 days	SIDIAP	2431205	30	1.23	2431281	<5	0.12	0.11	0.03	0.35	89%	65%	97%
14–29 days	BIFAP	5512096	60	1.09	5512401	11	0.20	0.19	0.10	0.36	81%	64%	90%
14–29 days	SIDIAP	1647562	38	2.31	1647799	<5	0.12	0.06	0.01	0.25	94%	75%	99%
2nd month (30–59 days)	BIFAP	6319646	129	2.04	6320759	14	0.22	0.11	0.06	0.19	89%	81%	94%
3rd month (60–89 days)	BIFAP	5253371	85	1.62	5254069	10	0.19	0.11	0.06	0.22	89%	78%	94%
4th month (90–120 days)	BIFAP	3358181	29	0.86	3358339	<5	0.06	0.07	0.02	0.29	93%	71%	98%
5th month (121–150 days)	BIFAP	1110766	<5	0.36	1110763	<5	0.27	0.77	0.17	3.43	23%	−243%	83%
6th month (151–180 days)	BIFAP	156824	<5	2.55	156881	<5	1.91	0.69	0.15	3.08	31%	−208%	85%

CASERTA: the Italian Caserta local health database; BIFAP: the Spanish Pharmacoepidemiological Research Database for Public Health System; SIDIAP: the Spanish Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària database; CPRD: the British Clinical Practice Research Datalink Aurum. HOp = Homologous primary vaccination Schedule; HEp = Heterologous primary vaccination schedule; HOb = Homologous booster dose; Heb = Heterologous booster dose; Control group = Non boosted adults; Exposed group = boosted adults; VE = Vaccine effectiveness; HR = Hazard ratio; IR = Incidence rates; adj. = Adjusted. The categories in which VE could not be estimated due to lack of sample size or number of cases are not reported in the table. Consequently, the number of person-days and cases do not sum up to the overall identified. Data reporting on less than 5 participants is not presented for privacy reasons.

dose in only one data source (ES-BIFAP), whereas the other data sources did not find enough sample size and episode occurrence. These are important real-world evidence about the vaccination benefits for these people, who are generally less represented in studies. The reduction of around 3–4 hospitalizations or 1–2 deaths with COVID-19 per 100,000 immunocompromised people per day attributable to the 3rd dose supports the recommendation to reinforce immunity with three doses as primary vaccination scheme in those people [40].

The short-term VE can lead to a highly complex decision-making process in a scenario characterized by fast-evolving variants. VE estimates were higher (but shorter in duration) with heterologous than homologous boosters (versus their respective controls) in both general and at potentially high risk of severe COVID-19 people. It is tempting to directly conclude that heterologous boosters provided higher VE than homologous ones. This may not be false, as observed from our results. However, this direct comparison may suffer from confounding due to vaccination prioritization and calendar time: people at high risk were more represented by homologous vaccinations (especially those > 60 years old) as heterologous schemes were not yet incentivized. As a strength, we compared boosted to unboosted individuals based on strict

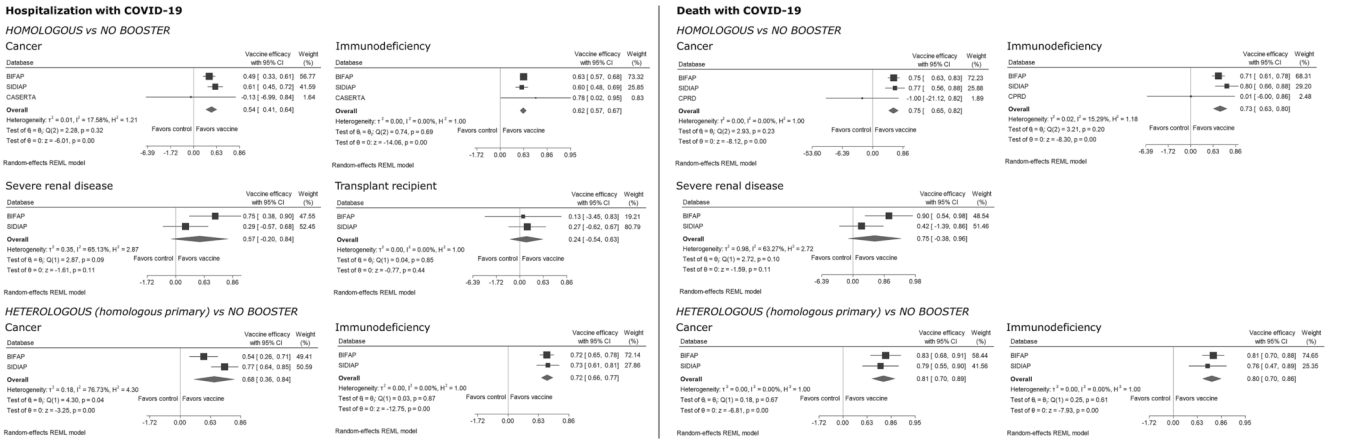

Fig. 2. Pooled Meta Analysis results for clinical subgroups.

matching conditions, limiting bias from different behavior, testing, and living settings, which is more likely to occur in studies with unvaccinated controls. Moreover, we provide additional evidence to the previous homologous and heterologous booster effectiveness studies, which mainly considered non-severe COVID-19-related outcomes [11,41–43].

Protection against death with COVID-19 during the Delta variant period was slightly higher than during Omicron within each boosted cohort, homologous and heterologous, and this is similar to estimations from previous studies [12,20,34,35,38]. However, our study could show evidence against the Omicron predominance only from one (Spanish) data source, and the VE duration was influenced by the limited follow-up data after booster vaccination, hampering longer precise estimations on the waning of immunity and protection during the Omicron period. Homologous boosters started to be administrated in September 2021 in Spain (71–86% of them in December 2021), approximately one month earlier than the heterologous ones, with the beginning of Omicron period negatively affecting the duration of the effectiveness of heterologous boosters. Important actions need to be taken to accelerate the update and availability of data to reach near real-time monitoring of effectiveness and benefit-risk assessment using observational data.

Some limitations must be recognized. Hospitalizations and deaths 'with' instead of 'for' SARS-CoV-2 infection were studied as outcomes, and those caused by other alternative reasons may not represent severe COVID-19. Those misclassifications would artificially decrease the estimated effectiveness. Also, we did not have the sensitivity of the cases definitions and its impact in the provided IR differences. Considering the expected timings for developing immunity after vaccination [44], the immediate VE that we observed during the first week can be hardly attributed to the intervention, thus requiring careful interpretation. Similar findings were also observed in other studies analysing the effectiveness of boosters in SARS-CoV-2 infections [11] and hospitalisation [45]. This effect may be mediated by less frequent testing in the vaccinated group immediate after vaccination as well as other potential confounders that could indicate uncontrolled differences in the baseline risk of COVID-19 diagnosis (for instance, not fully controlled healthy vaccinee effect as some controls may delay the booster dose when feeling sick or symptomatic). The potential immediate testing unbalance could disappear over time, as exhibited in a previous publication [11], allowing a cleaner VE estimation associated to the booster doses during the subsequent periods.

Unfortunately, the short follow-up (median between 9 and 16 weeks) did not allow to estimate the effectiveness later than 5 months in any cohort. Also, schemes from heterologous primary vaccinations were not sufficient in numbers for VE estimations in our study, thus, not all heterologous boosters benefitted from analyses with statistical precision. The use of the AZ booster was not sufficient to estimate its effectiveness. Considering death with COVID-19, the sample size was not sufficient to quantify the benefit of a booster among those initiating with AZ, which was initially recommended for younger populations.

Although the use of a common data model, protocol, and covariates selection, the evaluated outcomes could differ across the data sources. Spanish data sources captured most of the hospitalization and death with COVID-19 cases, the Italian only episodes of hospitalization, and the UK one only death with infection and homologous three doses information excluding hospitalization. Also, the proportion of hospitalisations or deaths 'with' or 'for' COVID-19 could vary among data sources. Countries also differ in the baseline characteristics of the matched populations, covariate availability and definition when based on hospital or primary care information, covered regions (which affect virus prevalence, predominance, public health recommendations to vaccinate and protect against infection, people's habits and beliefs, etc.), or calendar moments. Finally, we should consider that information on SARS-CoV-2 home-testing results was not available, so those people could have been misclassified as without prior infection.

5. Conclusions

In conclusion, we observed that heterologous or homologous 3rd mRNA doses offered additional protection to the two-dose schemes against death and hospitalization with COVID-19, regardless of the brand or the variant predominance periods, i.e., during Delta (Spain and UK) or Omicron (Spain). This finding was confirmed in aged adults and in people with immunodeficiency and cancer, adding important real-world evidence to clinical studies' observations. In line with other studies, we observed a wane in effectiveness in the early months that warrants further assessment of the benefit-risk against current and future variants, reinfections, and when a booster should be administered. The observed significant VE in the early post-vaccination period necessitates caution in the interpretation. As observed, boosters were effective in all age groups. Since benefit-risk is based on multiple factors, we recommend considering the VE estimation for each subgroup and period for specific public health and regulatory decision making.

6. Study Registration

EU PAS Register Number: EUPAS47725.

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Declaration of Competing Interest

All the authors declare financial support was provided by European Medicines Agency and the following financial interests/personal relationships which may be considered as potential competing interests: Elisa Martin Merino (corresponding author): Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) and Agencia Española de Cooperación Internacional para el Desarrollo (AECID) paid a presentation in a course 'Farmacovigilancia de las vacunas frente a la COVID-19'; Unpaid collaboration in observational studies with Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) for the "Grupo de Trabajo de Efectividad Vacunación COVID-19. Spanish Ministry of Health. ISCIII.CNE. Spanish Agency of Medicines and Medical Devices." Riefolo Fabio is an employee of TEAMIT Institute, consulting research company that participates in financially supported studies for European Medicines Agency and related healthcare authorities, pharmaceutical companies, and the European Union. Ylenia Ingrasciotta is the CEO of the academic spin-off "INSPIRE srl" of the University of Messina, which has received funding for conducting observational studies from contract research organizations (RTI Health Solutions, Pharmo Institute N.V.) and from pharmaceutical Companies (Chiesi Italia, Kyowa Kirin s.r.l., Daiichi Sankyo Italia S.p.A.). Karin Swart-Polinder is an employee of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for the government and related healthcare authorities and several pharmaceutical companies.

Data availability

We have shared the link to an open/public repository including the script we developed for programming and the code list defining the variables at the article: https://github.com/VAC4EU/CoVE-Public

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.10.011.

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