1. Title

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2. Abstract

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Effectiveness of heterologous and booster COVID-19 vaccination in 5 European countries, using a cohort approach in children and adults with a full primary COVID-19 vaccination regimen

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2.2. Keywords

COVID-19; vaccines effectiveness; heterologous and homologous vaccine schedule; booster; real-word data.

2.3. Rationale and background

Real-world effectiveness data demonstrated that COVID-19 vaccines' protection against severe SARS-CoV-2 infection is high in the short term but wanes over time, also depending on the virus variants. The vaccine effectiveness (VE) can vary depending on the vaccine brand or type (e.g., among mRNA or adenoviral platforms). Mixing brands for the primary vaccination and/or boosters (heterologous vaccination schedules) has been applied in different countries or regions although the effectiveness of heterologous schedules was not fully understood beyond immunogenic clinical data. With its increased ability to elude immunity and cause reinfections, the SARS-CoV-2 Omicron variant became dominant worldwide and led to the highest ever COVID-19 incidence, also in countries with high vaccination coverage, increasing as well hospitalization and severe outcomes cases in paediatrics populations, particularly in the presence of comorbidities. Moreover, only limited real-life data information on VE for children and adolescents in the EU is available. Further evidence about the VE of homologous (use of the same COVID-19 vaccine for the primary vaccination and booster dose) and heterologous (use of different COVID-19 vaccines for the primary vaccination or booster dose) vaccination schedules are needed both in adult ad paediatrics populations to keep fueling regulatory authorities' preparedness in case of urgent decision-making situations.

2.4. Research questions and objectives

To investigate the VE and waning of immunity of diverse COVID-19 primary vaccination (1st and 2nd doses) and booster (3rd dose) schedules with Comirnaty (PF), Spikevax (MD), and Vaxzevria (AZ) vaccines in preventing different COVID-19-related disease outcomes.

Primary objectives

1) To estimate the VE, and its waning, in adults (>17 years old) and adolescents (12-17 years old), separately, between heterologous and homologous primary vaccinations.
2) To estimate the VE, and its waning, in children (5-14 years old) between homologous primary vaccinations and non-vaccination.
3) To estimate the VE, and its waning, in adults and adolescents with full homologous primary regimen between those with a homologous booster and heterologous booster, separately, compared to those without any booster.
4) To estimate the VE, and its waning, in adults and adolescents with full heterologous primary regimen between those with any booster and those without any booster.

For patients free of prior COVID-19 infection (all analysis), that VE was estimated:

- By vaccine brand of the primary homologous scheme, the combinations in the heterologous scheme, and booster dose (3rd dose)
- By age categories.

- By time since a complete primary vaccination regimen (2nd dose receipt) or booster among the compared groups.
- Among clinical subgroups associated with a high risk of severe COVID-19 (immunocompromised patients and patients with cancer, transplants, severe renal disease, and Down syndrome).

For patients with prior COVID-19, the overall VE of different vaccination schemes against severe COVID-19 and COVID-19-related death was estimated.

Secondary objective

To estimate the VE against all-cause mortality in ≥60 years old adults with a full primary regimen (homologous or heterologous) between those with any booster and those without any booster. This estimation complements the results of COVID-19-related death of the primary objective.

2.5. Study design

Herein, we present a retrospective cohort study to estimate the VE of different COVID-19 vaccines schemes, and their waning, using different SARS-CoV-2 infection-related outcomes: (i) non-severe COVID-19, (ii) severe COVID-19, and (ii) COVID-19 with death. The study used data from 6 European different data sources and focused on the period ranging from the beginning of the vaccination campaign (December 2020) to the last data available from the participating data sources (ranging from December 2021 to February 2022). Thus, it mainly covered the Delta-Omicron predominant SARS-CoV-2 virus variant periods within the full vaccination regimen (first vaccination scheme and booster doses).

2.6. Setting

We retrospectively used data from 6 electronic health care databases in Southern, Northern, and Western Europe: the Italian Caserta local health database (IT-INSPIRE srl), the Italian Societa Servizi Informatici (IT-PEDIANET) database, the Spanish Pharmacoepidemiological Research Database for Public Health System (ES-BIFAP), the Spanish Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària (ES-SIDIAP) database, the Dutch PHARMO Database Network (NL-PHARMO), and the British Clinical Practice Research Datalink (UK-CPRD) Aurum.

Participants were matched 1:1 on the calendar date of the vaccination of interest (2nd vaccination-time0, for the primary vaccination scheme analysis; 3rd vaccination-booster-time0, for the booster vaccination analysis), the calendar date of the 1st vaccine dose, the vaccine brand of the 1st dose (Comirnaty, Spikevax, Vaxzervria), vaccinees age, sex, geographical region, clinical subgroup, and SARS-CoV-2 infection prior 1st vaccination dose.

For primary vaccination schedules, the date of cohort entry (time0) was the date when the participant received the 2nd dose. For the booster vaccinations, the date of cohort entry (booster-time0) was the date when the participant received the 3rd dose. For the non-boosted comparators, the same calendar date as the corresponding boosted-matched individual (booster-time0) was used for comparison.

Children and pre-adolescents were defined as "not vaccinated" until the date of the receipt of the 1st COVID-19 vaccine dose, thus, potentially selected as unvaccinated control.

Participants were considered to have a complete primary vaccination regimen when the record of a 2nd COVID-19 vaccine dose existed after more than 19 days from the 1st dose. Individuals were defined as "boosted" (homologous or heterologous) from the date of the 3rd COVID-19 vaccine dose receipt if at least 28 days after the 2nd one. Participants were defined as "non-boosted" until the date of 3rd vaccine dose administration, thus, potentially selected as non-boosted control. Among individuals with complete vaccination schemes, both homologous/heterologous primary vaccinations and booster/non-boosted cohorts were identified separately.

Statistical data analyses

Inverse probability weighted (IPW) Cox models (CI, 95%) have been used to derive the average hazard ratio (HR) of COVID-19-related outcomes. The adjusted VE (%) values were estimated as 1 minus the adjusted HR multiplied by 100. Various covariates have been considered potential confounders for the IPW.

The VE for each matched cohort was estimated by (*i*) vaccine brands, (*ii*) time after vaccination, (*iii*) age categories, (*iv*) high-risk of severe COVID-19 clinical subpopulations (for the participant databases able to identify them through diagnosis or medications prescriptions, (*v*) and SARS-CoV-2 infection before vaccination, and (*vi*) dominant SARS-CoV-2 variants (defined as the variant reaching 50% of the total sequenced specimens at (booster-)time 0). Three main SARS-CoV-2 variants' periods have been identified (pre-Delta, Delta, and Omicrons) specifically for each participating country.

Random-effects meta-analyses, using the main estimates against severe COVID-19 outcomes from each data source, were performed for clinical subgroups for both adult and children populations. Sensitivity analysis restricting to patients with prior SARS-CoV-2 negative tests was performed to control for surveillance bias.

2.7. Subjects and study size

Study Population

The source population comprises all children, adolescents, and adults registered in any of the data sources during the study period (December 2020 -February 2022 for ES-BIFAP and IT-INSPIRE and -December 2021 for the other data sources). Eligible study participants had at least 2 years of available healthcare data. The vaccinated study population includes all individuals with at least two recorded vaccinations since the start of the study period.

Study size

The study cohorts contained more than 20 million adolescents and adults with a complete primary vaccination scheme (1st and 2nd dose receipt) and 3 to 6 months of follow-up across all the participating data sources. We could match ≈24-51% of the population for the heterologous vaccination scheme (comparator) and ≈0.5-1.5% for the homologous scheme. The majority of adults and adolescents were free of SARS-CoV-2 infection prior to vaccination (58-95% across the total matched population for all the data sources).

During the study period, approximately 308,000 children with around 3 months of follow-up were vaccinated with two doses and included in the study across all the participating data sources. Based on the matching criteria, a total of 295,573 children were matched for the primary vaccination schedule (95% of the total children). Of the matched children, the main population (97%, 287,050 children) did not have encountered prior SARS-CoV-2 infection.

2.8. Variables and data sources

Data sources captured vaccination and outcomes from hospitalization and/or general practice and/or test registries. This study considered different outcomes related to COVID-19: non-severe SARS-CoV-2 infection, hospitalized COVID-19 (severe), COVID-19 with death, and all-cause mortality (secondary objective). The main exposure of interest was the receipt of a different primary regimen or booster COVID-19 vaccine (receiving the same 1st dose brand), the dose, and its brand. Selection of covariates, primary care physician' visits, clinical conditions, and medication use (including influenza vaccination among others), were collected up to 2 years before (booster-)time 0 (or 7 days before, for visits to control by healthy vaccinees effect) and considered as potential confounders for the IPW.

2.9. Results

The shown VE percentages are statistically significant and reported in ranges of values across the data sources, otherwise, the mention of non-statistically significance is specified.

Primary Objectives

Adults, Primary Vaccination

Among 89,528 adults' matched pairs, overall, homologous primary vaccinations showed a slightly decreased VE (-27% to –36% by data source) compared to heterologous regimens against **non-severe COVID-19**, mostly receiving AZ as the first dose (VE ranged from -43% to –27% across data sources). By time since vaccination, or, by age categories, no clear patterns were found. In ES-BIFAP, the lower VE with homologous was more marked during the Delta (-39%) than the Omicron (–24%) periods. No differences between homologous and heterologous regimens were observed for

severe COVID-19 (estimated in Spanish data sources) and no sufficient cases of **death with COVID-19** were found to analyse.

Adolescents, Primary Vaccination

We matched 1,329 pairs among adolescents. Considering non-severe COVID-19, no differences were found in the VE estimates comparing homologous versus heterologous primary vaccinations. The small sample size hampered the VE estimation related to the other severe outcomes.

Children, Primary Vaccination

287,000 children without prior COVID-19 were matched. Considering **non-severe COVID-19**, homologous primary two doses of both the mRNA vaccines (PF or MD) showed VE, varying from 29% to 77% across data sources, during the Delta predominant variant period, when compared to unvaccinated individuals. VE remained 4-5 months. During the Omicron predominance, VE decreased from 77% to 42% in IT-INSPIRE and reverted to an increased risk of non-severe SARS-CoV-2 infection, from 29 to -44%, in ES-BIFAP. Estimates did not show protection among children with prior SARS-CoV-2 infection. The protection against **severe COVID-19** was >90% in ES-SIDIAP (during the Delta period) and ≈50% in ES-BIFAP for PF vaccine versus unvaccinated individuals. In ES-BIFAP, VE during the Delta period was 61%, but non-statistically significant, and 50% during the Omicron period. No data for waning of immunity, from other data sources, vaccine brands and COVID-19 with death were available.

Adults, Booster Vaccination

5.6 million adults without prior SARS-CoV-2 infection were matched. 79,076 cases of **non-severe COVID-19** among boosted versus 138,638 among unboosted adults were captured in 5 data sources. VE against non-severe COVID-19 ranged 31-69% for homologous boosters and 42-70% for heterologous boosters across data sources, independently from the vaccine brand. Considering **severe COVID-19**, 1,015 cases among boosted versus 3,362 among comparators were captured in 3 data sources with hospitalization information (mostly in ES-BIFAP and ES-SIDIAP and a few in IT-INSPIRE). Against severe COVID-19, heterologous boosters (homologous doses 1 and 2), independently from the vaccine brand, showed a VE of 73-81% across data sources whereas homologous boosters have a VE of 42-67%, compared to their respective unboosted controls. Considering **death with COVID-19**, 313 cases of death with COVID-19 among adults who received any booster versus 1,367 among comparators were captured (mostly in ES-BIFAP and ES-SIDIAP and a few in UK-CPRD). Protection against death with COVID-19 was similar among homologous and heterologous schemes (70-88% across schemes and data sources). Duration of immunization varied from 1 to 6 months across data sources and events, independently of the booster schedule. Considering both, severe COVID-19 and death outcomes, no clear VE differences were identified during both the Delta and Omicron periods across data sources. In patients with **cancer**, effectiveness against severe COVID-19 ranged from 54% to 77% with heterologous and from 49% to 61% with homologous boosters across data sources, whereas in patients with **immunodeficiency** VE was between 60-78% with any scheme. Among patients with prior SARS-Cov-2 infection, VE against severe COVID-19 was 69% (ES-BIFAP) and 71% (ES-SIDIAP) for heterologous and 43% (ES-SIDIAP) for homologous 3 doses schemes. VE against death with COVID-19 was 92% (ES-BIFAP) for heterologous and 68% (ES-SIDIAP) for homologous boosters in these patients.

Adolescents, Booster Vaccination

We matched 17,652 adolescent pairs of which 408 cases of **non-severe COVID-19** among boosted versus 936 cases among unboosted individuals were captured in 5 data sources (ES-BIFAP, ES-SIDIAP, IT-INSPIRE, UK-CPRD and NL-PHARMO). Among adolescents with a homologous primary vaccination, the VE of homologous booster doses against non-severe COVID-19 varied from 35-67% across vaccine brands and data sources, whereas VE of heterologous boosters was 48% in ES-BIFAP (the only data source in which heterologous boosters were found) for PF as 1st and 2nd dose, and MD as 3rd dose, when compared to the respective unboosted controls. During the Delta predominance period, VE was only observed in Italy (69%) for homologous boosters. During the Omicron predominance, VE varied from 67% (IT-INSPIRE) to 44% (ES-BIFAP) for homologous boosters whereas, for the heterologous ones, was 51% (ES-BIFAP). VE for the homologous boosters lasted up to one month in Italy (75%; later on, <5 cases occurred) and two months in Spain (45%). Heterologous primary vaccinations (in UK-CPRD) were not sufficient to be analysed. No VE was

estimated for **severe COVID-19 and death with COVID-19** outcomes due to the low number of cases (<5).

Sensitivity Analysis

Balancing by any prior testing, the VE against **non-severe** infection remained 57-59% for primary vaccination among children and 30-55% for boosters in adults. Against **severe** COVID-19, VE remained moderate (55-59%) for homologous boosters and high (70-81%) for heterologous boosters. Against **death with COVID-19,** VE was 67-79% for homologous and 77-81% for heterologous boosters among adults.

Meta Analysis

In adults, the pooled VE of **homologous boosters against severe COVID-19** was 62% (95% CI: 57 to 67%; I^2=0%) among subjects with immunodeficiency, 54% (95% CI: 41 to 64%; I^2=18%) among patients with cancer, 24% (95% CI: -54 to 63%; I^2=0%) among patients with a transplant and 57% (95% CI: -20 to 84%; I^2=65%) among those with severe renal disease. Additionally, the pooled VE of **homologous booster against death with COVID-19** was 73% (95% CI: 63 to 80%; I^2=15%) among immunocompromised patients, 75% (95% CI: 65 to 82%; I^2=0%) among patients with cancer, and 75% (95% CI: -38 to 96%; I^2=63%) for those with severe renal disease.

The pooled VE of **heterologous boosters against severe COVID-19** (homologous primary vaccination) was 72% (95% CI: 66 to 77%; I^2 =0%) among adults with immunodeficiency and 68% (95% CI: 36 to 84%; I^2 =77%) for adults with cancer. In addition, the pooled VE of **heterologous boosters against death with COVID-19** was 80% (95% CI: 70 to 86%; I^2 =0%) among immunocompromised patients and 81% (CI=95% CI: 70 to 89%; I^2 =0%) among those with cancer.

Among children, the pooled VE of **primary vaccination against severe COVID-19** in the Delta predominance period, was 82% (95% CI: -10 to 97%; I^2=62%) in Spain.

Secondary Objective (any cause of death)

In patients aged ≥60 years old, the VE against any cause of death for any booster dose (whether homologous or heterologous), following a homologous primary vaccination schedule, ranged between 72% and 96% across 10-by-10 age categories and data sources (ES, UK and NL). VE was higher during the Delta (75% for homologous and 83% for heterologous boosters) than the Omicron variant period (67% for both booster types). A few heterologous primary vaccinations were used, showing effectiveness (74%) only in 80+ years old in UK.

2.10. Discussion

Using real-world data from 6 different databases in Europe, various schemes of COVID-19 vaccination (primary vaccination and booster doses) were identified among adults, adolescents, and children (only in 3 countries) in Spain, Italy, the Netherlands, and the UK from the beginning of the vaccination campaign to December 2021 or February 2022 (in Italy and Spain).

Most of the **adults** participating in our study were fully vaccinated from mid of 2021 and received booster doses in the last months of 2021. Under the scenario of a reported very high level of protection with the homologous COVID-19 vaccination during Delta predominance in the EU/EEA countries, in the current project, slightly higher effectiveness of heterologous versus homologous primary vaccinations against **non-severe** COVID-19 was observed in patients who received an AZ first dose and a 2nd mRNA dose in comparison to those receiving two AZ doses. VE was not different among people who mixed mRNA doses. This is in accordance with previous clinical trial studies and supporting the public health recommendation to switch to mRNA platforms after AZ vaccines in some countries. Against **severe COVID-19**, VE was not different between heterologous and homologous primary vaccinations administrated in the same calendar moments, and not enough cases of COVID-19 with **death** occurred for VE estimation. No clear diverse patterns of the waning of immunity for homologous versus heterologous primary schemes, or changes in the comparative effectiveness among age groups or variant predominance periods were observed. This is also due to the small sample size that contributed to this primary analysis.

The protection with a **booster** against **non-severe COVID-19** showed **important variations** (28-74%) by brand and/or country. Effectiveness was high for AZ boosters in the UK, medium for PF or MD in Italy, the UK, and The Netherlands, and very low for all the brands in Spain (that did not improve after balancing testing in sensitivity analyses). Variations can result from different clinical characteristics of the populations at the analysed moment: the regions (with different virus prevalence, predominance, and potential public health recommendation, health assistance or people habits, etc.) among others. **mRNA-boosted** adults with PF and MD showed high effectiveness **against severe COVID-19 and death with COVID-19** regardless of the brand of the two doses administrated as primary vaccination. Those results were more solid in Spanish cohorts probably due to the higher use of those mixed schemes. The booster doses were observed effective during both Delta (Spain and UK) and Omicron (Spain) periods supporting the public health recommendations for subsequent boosters during the Omicron era. VE remains apparently longer for the homologous booster (until the 2nd or 5th month) than the heterologous (until the 1st or 3rd month) that started to be administrated approximately one month later. This reduction of the VE could be triggered by both the waning of immunity and lower effectiveness against the more aggressive Omicron variant. The effectiveness against death with COVID-19 remained until enough number of cases were detected, with a maximum duration of 5-6 months in a Spanish data source. Although the reason to die during the study period was unknown and many could have died by other reason than COVID-19, all-cause mortality analyses' results complemented the effectiveness of booster doses found against death with COVID-19 that would include missing cases without SARS-COV2 test in the main analysis.

A good sample size of **patients with immunosuppression, cancer, and severe renal disease** was achieved among those who received homologous primary schemes. According to pooled estimates, patients with immunocompromised or cancer benefited substantially from a booster (homologous or heterologous) considering both the severe outcomes (VE ranged from 54% to 75%, low or no heterogeneity). Also, high VE of homologous boosters was observed against severe outcomes in adult patients with severe renal disease in one (ES-BIFAP) out of three data sources tested. These findings add values for understanding the vaccination outcomes in those clinical subgroups that are less represented in randomized control trials (RCT) and small studies.

Most of the **adolescent** individuals completed the primary vaccination during the Autumn of 2021 with homologous mRNA vaccines, the only approved for such young populations. Thus, the matched heterologous cohorts were insufficient to estimate compared VE. Then, three doses of PF showed moderate VE against non-severe COVID-19 in Italy (VE: 67%) both during Delta and Omicron, as well as three homologous Moderna doses in Spain (VE: 64%) in comparison with similar two doses without a booster. In Spain, the observed moderate effectiveness was only significant during the Omicron period, where Moderna could have been more used. Early boosted adolescents at high risk of infection or related comorbidities, inferior infection notification rates during the last months studied, frequent patients with prior infection along the time and/or more underlined prior infections in the control groups could be playing a crucial role in such reduced estimates. Also, the VE of a 3rd homologous dose was moderate among Italian adolescents who were immunocompromised, adding value to the vaccination recommendation at that moment. No severe COVID-19 or death with COVID-19 cases occurred for permitting the VE estimation among adolescents.

For **children**, data from Spain and Italy showed that most of them completed their primary vaccination scheme in February 2022. Among them, varying effectiveness was shown (from low to high) against non-severe SARS-CoV-2 infection during the **Delta variant** predominance period. **During the Omicron period**, VE decreased in Italy and Spain (the last with an even higher risk of infection among vaccinated children as consequence of differential surveillance/testing between vaccinated and unvaccinated children as observed in the sensitivity analysis). Overall, effectiveness decreased in magnitude over time. The increased incidence of the infection in all age groups from December 2021, the consequence of the onset of the Omicron variant, the relaxation in Public Health measures as it was considered a less severe variant, the potential underestimation of the infection incidence due to non-reported positive self-COVID-19-tests and other factors aforementioned for adolescents, could have also triggered the reduced VE among the youngest. A complete primary vaccination regimen offered a moderate-high level of protection for **severe COVID-19** in children (12-14 years old, as no cases occurred in those 5-11) in Spain. The database producing that moderate effectiveness showed differential COVID-19 severity misclassification in a manual review independent of the current project. Hospitalisations among non-vaccinated were more often confirmed due to COVID-19 (63%) than among vaccinated individuals (24%). This suggests that the

actual effectiveness would be higher than estimated. In the Omicron period, vaccination showed moderate protection against severe disease, as reported (49%; 95% CI: 26-64%) among people aged 12-17 years in February 2022 in Spain after suffering a decreasing trend from November 2021 (previously, up to October 2022, VE was kept ≥90%) (isciii report). There were no deaths related to COVID-19 disease among children, as in previous studies.

2.11. Conclusions

The real-world evidence effectiveness of EU-approved PF, MD, and AZ COVID-19 vaccines and their combination in different schemes was assessed in this study during the Delta and the early Omicron circulating variants. Our results support health institutions' recommendation of mixing different vaccine brands for the second dose, particularly for those vaccinated with AZ first, as no threatening VE differences were found across homologous and heterologous primary vaccination schemes against severe and non-severe events. This is in line with previously small published clinical trials. Independently of the vaccination history, mRNA 3rd doses offered clear protection against severe post-infection events, both, in the general adult population and more vulnerable subjects, adding evidence for these subjects at higher risk and supporting previous observations in clinical studies for adults. We observed a wane of immunity from the early months post-vaccination. Our data infer that full primary vaccination protected 12-14-year-old children against hospitalized COVID-19 disease during the Delta and Omicron variant periods in Spain, including immunocompromised children. No clear conclusions are available for 5-11 years old vaccinees as no severe cases were encountered. Thus, broader and ad-hoc studies for children are further needed. Beyond the evidence of the COVID-19 vaccine herein reported, useful for the benefit-risk assessment, a cautious interpretation of these results should consider a broad reduction in infection notifications from the last months of 2021 due to self-testing at home, the vaccination campaign differences across countries and aforementioned limitations. These conclusions cannot fully address the current virus epidemiological situation with updated PF and MD vaccines with Omicron subvariants. Therefore, updated effectiveness estimations in all age groups on severe reinfections are required.