Covid Vaccines Effectiveness (CoVE)

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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1. Participants and Descriptive data: Matched Adults and Adolescents for effectiveness of primary vaccination

Among the total study individuals with heterologous and homologous primary vaccination schemes identified in the data sources, more than **20 million ≥12 years** old individuals, (Figure A1; Section 10.15.1), we could have respectively matched around **24-51% of the heterologous vaccination individuals and around 0.5-1.5% of the homologous vaccinated individuals** among all the participating databases (ANNEX 1, Tables A2).

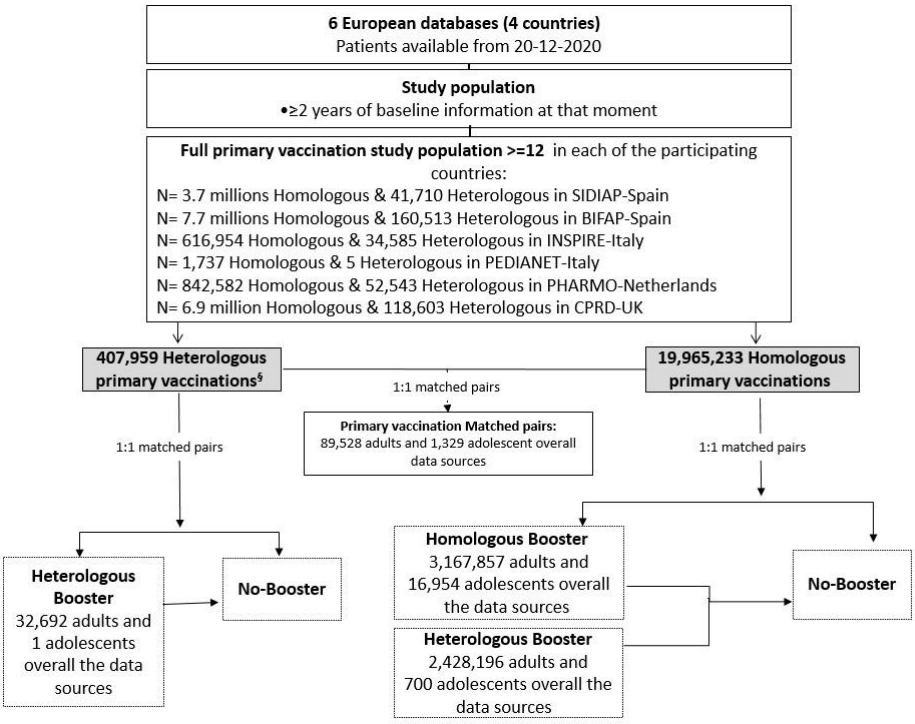

Figure A1. Ascertainment of full primary vaccination adults and adolescent study population and compared cohorts.

For the adult (>17 years old) matched homologous and heterologous population, the vaccine brand monthly distribution of the administered first dose is shown in Tables A3 (ANNEX 1). Overall, across all the databases, the individuals' pairs receiving the AZ vaccine as the first dose showed the highest percentage distributed from April to November 2021. PF vaccine as administered first dose started to be significantly registered from November 2021 to February 2022 in all the DAPs except for the UK, where the intake distribution clearly represents the period in which an mRNA vaccine administration was recommended in this country.

For the adolescent (12-17 years old) matched homologous and heterologous population, the vaccine brand monthly distribution of the administered first dose is shown in Tables A4 (ANNEX 1). PF vaccine was the main administered vaccine brand reported for this sub-population and its administration significantly appears in August 2021 until the end of the database's follow up period (December 2021- February 2022). Spain registered a significant number of PF doses administered in August-October 2021, with some cases of MD mainly reported in September 2021.

The baseline characteristics of the **adults** (>17 years old) not suffering from Covid-19 prior vaccination (58-95% among databases of total ≥12 years old study population), belonging to the final compared heterologous and homologous primary vaccination schemes (1st and 2nd dose) cohorts are listed in Tables A5 (ANNEX 1). Overall, we evaluated more than 89,500 adult pairs across all the participating databases who were included in the effectiveness analysis for

the primary vaccination scheme. PEDIANET-Italy data does not present matched adults and is excluded from this analysis. The percentage of matched adults receiving AZ or PF as the first vaccine dose significantly varies across countries (ANNEX 1 Tables A5). Differently, the distribution of the Moderna vaccine is less variable across databases, not exceeding 9%. More specifically, we can observe this distribution of the first dose administered vaccine brand for each DAP in matched adults prior to SARS-Cov-2 infection:

AZ:
- SIDIAP-Spain: 91%
- BIFAP-Spain: 62%
- INSPIRE-Italy: 99%
- PHARMO-Netherlands: 20%
- CPRD-UK: 52%

MD:
- SIDIAP-Spain: 2.1%
- BIFAP-Spain: 5.6%
- INSPIRE-Italy: <5 individuals
- PHARMO-Netherlands: 8.9%
- CPRD-UK: 3.6%

PF:
- SIDIAP-Spain: 6.6%
- BIFAP-Spain: 32%
- INSPIRE-Italy: 1%
- PHARMO-Netherlands: 71%
- CPRD-UK: 44%

Median time to follow-up ranges from 11 to 198 days. The follow-up finalization is due to the censoring of the other member of the pair in 16-52% of the cases across all the data sources, the 3rd dose administration in between 4.5-50% of the cases, and the study exit date in 2.4-48% of the cases. A gender balance of around 50% is maintained across all the DAPs, where the mean age for adults ranged from 38 (INSPIRE-Italy) to 67 (PHARMO-Netherlands) years old. Comorbidity and comedication are balanced among the compared groups across DAPs. Among the solicited comorbidities, a significant subgroup of more than 12,400 total adult pairs with immunodeficiency disorders has been found across databases. The total number of pairs with immunodeficiency or under immunosuppressant drugs across all the participant data sources is around 24,480, ranging from 2.7% to 39% of the total matched adults among different DAPs. The lowest percentage (2.7%) is represented in CPRD-UK, 10-16% in BIFAP-SIDIAP, and the highest percentage (39%) is in INSPIRE-Italy or (37%) PHARMO-Netherlands. Other clinical subgroups were too low for the analytical stratification herein applied.

The baseline characteristics of **adolescents** (12-17 years old), not suffering from Covid-19 prior vaccination, who contributed to the final compared heterologous and homologous primary vaccination scheme (1st and 2nd dose) cohorts are listed in Tables A6 (ANNEX 1). Matched adolescents were low in number compared to adults (around 1,330 matched pairs). That is because heterologous schemes were rarely used among them. Spanish data sources, BIFAP and SIDIAP, and CPRD-UK were the ones providing the highest numbers, with 967, 221, and 130 pairs, respectively, which participated in the effectiveness analysis of the different primary vaccination schemes. INSPIRE-Italy did not present any matched adolescent without prior Covid-19. In PEDIANET-Italy and PHARMO-Netherlands only <5 and 8 pairs were matched, respectively. Across Spanish and UK study individuals, PF vaccine is the most frequently administered first dose (50-84%), followed by MD. 50% of the adolescent pairs in CPRD-UK received AstraZeneca. Median time to follow-up ranged from 18 to 179 days. The follow-up finalization is due to the censoring of the other member of the pair in 27-65% of the cases across all the data sources, the 3rd dose administration in between 0-17% of the cases, and the study exit date in 35-72% of the cases. A gender balance of around 50% is maintained across all the DAPs. Mean age across the total matched cohort is around 14-16 years old. Other clinical subgroups are minimal in number.

2. Participants and Descriptive data: Matched Children for effectiveness of primary vaccination

Children and pre-adolescent pairs (5-14 years old) without Covid-19 prior vaccination across all the participating data sources were selected for main effectiveness analysis. Overall, we have been able to match more than 287,000 individuals with unvaccinated controls (Figure A2 and Tables A14; ANNEX 1):

- BIFAP-Spain: 177,921 homologous and 668 heterologous children
- SIDIAP-Spain: 75,276 homologous and 85 heterologous children
- INSPIRE-Italy: 14,236 homologous and <5 heterologous children
- PEDIANET-Italy: 1,566 homologous and 5 heterologous children
- PHARMO-Netherlands: 17,293 homologous and <5 heterologous children
- CPRD-UK: no homologous and heterologous children

The most administered vaccines in the **homologous children's** cohorts have been PF (>90% SIDIAP-ES, BIFAP-ES, PHARMO-NL, INSPIRE-IT, and >77% PEDIANET-IT), mainly distributed in September 2021, January and February 2022. Children with an **immunodeficiency** condition or under immunosuppressant medications remain significantly represented in the homologous cohorts of SIDIAP (21%) and BIFAP-Spain (11%), and INSPIRE-Italy (32%) and contributed to VE in those clinical subgroups. Other clinical subgroups were not sufficiently represented to be analyzed (around <10% in each compared group). The youngest vaccinated children (aged 5-11 years) were only sufficiently represented in the Southern countries (particularly 34,520 in BIFAP-Spain and 3,325 in INSPIRE-Italy). This age subgroup was analyzed in a separate stratum. The other stratified analysis by duration of immunity and clinical subgroups were analyzed for the entire pool of children vaccinated at age 5-14 and matched controls. Details are provided in Tables A14 (ANNEX 1).

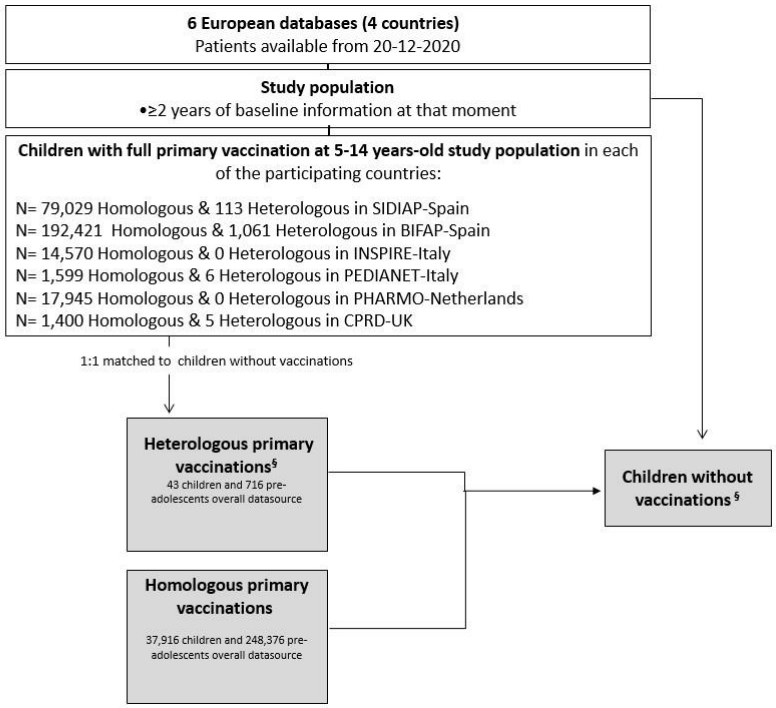

Figure A2. Ascertainment of children with full primary vaccination study population and compared cohorts.

3. Participants and Descriptive data: Matched Adults for booster evaluation

For the total adult-matched population, monthly distribution of the administered booster doses stratified by vaccine brand is shown in Tables A10 (ANNEX 1). The 3rd dose administration started in September 2021 and the most frequently administered vaccine brand was PF across all countries, including the UK. For the main effectiveness analysis, only **pairs without Covid-19 prior vaccination** were included (Figure 6), and are described in Tables A7, A8 and A9 (ANNEX 1) by type of primary scheme:

1) The baseline characteristics of the **adults** belonging to the matched homologous booster and non-booster cohorts with a **homologous primary vaccination (3 doses of the same vaccine brand** versus only 2 doses) are listed in Tables A7 (ANNEX 1). Data are available from all the participant data sources except for PEDIANET-Italy.

Overall, more than 3.1 million pairs have been counted among all countries for these homologous cohorts, most of them belonging to the PF vaccine brand subgroup:

- BIFAP-Spain has 1,522,416 pairs (AstraZeneca: <0.1%, Moderna: 13%, Pfizer: 87%)
- SIDIAP-Spain has 356,790 pairs (AstraZeneca: <0.1%, Moderna: 22%, Pfizer: 78%)
- INSPIRE-Italy has 218,106 pairs (Moderna: 20%, Pfizer: 80%)
- CPRD-UK has 1,029,806 pairs (AstraZeneca: 0.4%, Moderna: <0.1%, Pfizer: 100%)
- PHARMO-Netherlands has 40,739 pairs (AstraZeneca: 35%, Moderna: 9.7%, Pfizer: 56%)

Women accounted for 52-59% of total individuals across data sources, and mean age ranged from 52 to 75 years old. Booster doses were mainly received in September-December 2021. The median time to follow-up was about 2 weeks (11-16 days) since most non-boosted comparators received the 3rd vaccine dose during this time window, triggering the censoring of the matched pair. Individuals with immunodeficiency or cancer diagnosis were significantly represented subgroups, with a total of around 460,000 and 220,000 pairs among all data sources, respectively. Other comorbidities and comedications were quite balanced between the homologous boosted and non-boosted cohorts.

2) Baseline characteristics of the **adults** belonging to the compared **heterologous booster and non-booster cohorts** with a **homologous primary vaccination** (same brand for the first two vaccine doses, but different brand for the 3rd dose) are listed in TABLE A9 (ANNEX 1). Data are available for SIDIAP- and BIFAP-Spain, INSPIRE-Italy and PHARMO-Netherlands data sources.

More than 2,428,000 pairs were matched, most of them receiving PF as the 1st vaccine brand dose. The most commonly administered 3rd doses were MD:

- BIFAP-Spain contributed 1,303,411 pairs
  - Homologous primary scheme; AstraZeneca: 48%, Moderna: 3.8%, Pfizer: 48%
  - 3rd dose; AstraZeneca: <0.1%, Moderna: 75%, Pfizer: 25%
- SIDIAP-Spain has 850,525 pairs
  - Homologous primary scheme; AstraZeneca: 44%, Moderna: 0.2%, Pfizer: 55%
  - 3rd dose; AstraZeneca: <0.1%, Moderna: 99%, Pfizer: 1.4%
- INSPIRE-Italy has 186,775 pairs
  - Homologous primary scheme; AstraZeneca: 39%, Moderna: 1.0%, Pfizer: 60%
  - 3rd dose; Moderna: 86%, Pfizer: 14%
- PHARMO-Netherlands has 87,485 pairs
  - Homologous primary scheme; AstraZeneca: 20%, Moderna: 2.6%, Pfizer: 78%
  - 3rd dose; AstraZeneca: 0.4%, Moderna: 90%, Pfizer: 9.8%

Women accounted for around 52-56% of total individuals in this analysis in all data sources. Mean age ranged from 53 to 70 years old, similar to the corresponding homologous cohorts. Booster doses were mainly administered in October 2021-February 2022. The median time to

follow-up was less than 2 weeks (6-14 days) since most of the non-boosted comparators received the 3rd vaccine dose during this time window, triggering the censoring of the matched pair. Comorbidities and comedication were quite balanced between the booster and non-booster cohorts, although smaller percentages in many factors were observed compared to the corresponding boosted homologous cohort.

3) Baseline characteristics of the **adults** belonging to the compared booster and non-booster cohorts with a **heterologous primary vaccination** are listed in Tables A8 (ANNEX 1). Data are available from all the participant data sources except for PEDIANET-Italy.

Overall, more than 32,600 pairs have been counted across all countries for these heterologous cohorts, most of them receiving the AZ vaccine brand as the 1st vaccine brand dose. The most commonly administered 3rd doses were MD in Spain and the Netherlands, and PF in Italy and the UK:

- BIFAP-Spain has 5,801 pairs
  - 1st dose; AstraZeneca: 87%, Moderna: 3.8%, Pfizer: 9.7%
  - 3rd dose; AstraZeneca: 0.2%, Moderna: 59%, Pfizer: 41%
- SIDIAP-Spain has 3,414 pairs
  - 1st dose; AstraZeneca: 99%, Pfizer: 0.8%
  - 3rd dose; Moderna: 91%, Pfizer: 8.9%.
- INSPIRE-Italy has 15,236 pairs
  - 1st dose; AstraZeneca: 100%
  - 3rd dose; Moderna: 6.5%, Pfizer: 94%
- CPRD-UK has 7,248 pairs
  - 1st dose; AstraZeneca: 51%, Moderna: <0.1%, Pfizer: 49%
  - 3rd dose; AstraZeneca: 7.3%, Moderna: 7.7%, Pfizer: 85%
- PHARMO-Netherlands has 993 pairs
  - 1st dose; AstraZeneca: 63%, Moderna: 14%, Pfizer: 22%
  - 3rd dose; AstraZeneca: 2.5%, Moderna: 62%, Pfizer: 35%

Women were around 48-62% across data sources. Mean age ranged from 36 to 67 years old, which is lower compared to the corresponding homologous cohorts. Booster doses were mainly administered in October 2021-January 2022. The median time to follow-up was less than 2 weeks (7-11 days), since most of the non-boosted comparators received the 3rd vaccine dose during this time window, triggering the censoring of the matched pair. Clinical subgroups in this booster heterologous cohort were less represented compared to individuals receiving homologous booster doses. Other comorbidity and comedication were quite balanced between the booster and non-booster cohorts, although reduced numbers in many factors are observed compared to the corresponding boosted homologous cohort.

4. Participants and Descriptive data: Matched Adolescents for booster evaluation

For the total adolescent population, monthly distribution of the administered booster doses stratified by vaccine brand is shown in Tables A11 (ANNEX 1). The 3rd dose administration peaked between October-November 2021 with a more balanced PF-MD frequency of administration across all countries than adults. The study populations include adolescents aged 12-17 years old. Booster doses analyses were not planned during the protocol design since we did not expect adolescents receiving booster doses to be available during the study period. However, enough descriptive number were captured from some DAPs and are reported in this section. Based on the primary schemes (heterologous or homologous), the booster dose schemes have been matched with corresponding non boosted adolescents.

For effectiveness of booster among **adolescents'** pairs, free of Covid-19 prior vaccination (main analysis), the booster (Figure 6) and non-booster cohorts are described in Tables A15, A16 and A17 (ANNEX 1) by type of primary scheme and below:

1) Baseline characteristics of the **adolescents** belonging to the final matched **homologous booster** and non-booster cohorts with a homologous primary vaccination are listed in Tables 15 (ANNEX 1). Data are available from all the participant data sources except for PEDIANET-Italy (only 76 person-days).

Overall, more than 16,950 pairs have been counted across all countries for these homologous cohorts, most of them belonging to the PF vaccine brand subgroup:

- BIFAP-Spain has 2,086 pairs (Moderna: 9.9%, Pfizer: 90%)
- SIDIAP-Spain has 376 pairs (Moderna: 1.9%, Pfizer: 98%)
- INSPIRE-Italy has 12,939 pairs (Pfizer: 100%)
- CPRD-UK has 1,355 pairs (Pfizer: 100%)
- PHARMO-Netherlands has 198 pairs (Pfizer: 100%)

Women were around 49-56% across data sources. Booster doses were mainly received in November-December 2021 and January 2022. The median time to follow-up varies from 8 to 91 days. Individuals with immunodeficiency or cancer diagnosis were validly represented subgroups, with a total of 14-61% among the matched population (14%, PHARMO; 34% INSPIRE; 20% BIFAP; 61% SIDIAP).

2) Baseline characteristics of a**dolescents** the final compared booster and non-booster cohorts with a **homologous primary vaccination and a heterologous booster** (identical first two vaccine doses, but different 3rd dose) are listed in Tables A17 (ANNEX 1).

Only few subjects' data are available for SIDIAP- and BIFAP-ES, and INSPIRE-IT, most of the patients received the PF vaccine brand as the 1st vaccine brand dose except for INSPIRE-IT (85% MD). The most commonly administered 3rd doses are MD, except for INSPIRE-IT (85% PF):

- BIFAP-Spain has 517 pairs
    - Homologous primary scheme; Moderna: 14%, Pfizer: 86%
    - 3rd dose; Moderna: 86%, Pfizer: 14%
- SIDIAP-Spain has 141 pairs
    - Homologous primary scheme; Pfizer: 100%
    - 3rd dose; Moderna: 99%, Pfizer: 1%
- INSPIRE-Italy has 40 pairs
    - Homologous primary scheme; Moderna: 85%, Pfizer: 15%
    - 3rd dose; Moderna: 15%, Pfizer: 85%

Women were around 50-60% across data sources. Booster doses were mainly received in December 2021-February 2022. The median time to follow-up varies from 11 to 86 days. Due to the low number of subjects, comorbidities and comedication were not significantly represented in this study cohort.

3) Baseline characteristics of **adolescents** for final compared booster and non-booster cohorts with a **heterologous primary vaccination** are listed in Tables A16 (ANNEX 1). No sufficient data (≥ subjects) are available for any of the data sources.