

Real-world-evidence on different COVID-19 vaccines combinations' effectiveness in six electronic healthcare data sources from four pan-European countries

Fabio Riefolo^{1,2}, Belén Castillo Cano³, Mar Maria Martin³, Davide Messina⁴, Roel Elbers⁵, Dorieke Brink-Kwakkel⁵, Felipe Villalobos⁶, Ylenia Ingrasciotta⁷, Patricia Garcia-Poza³, Karin Swart-Polinder⁸, Patrick Souverein⁹, Luis Carlos Saiz¹⁰, Carlo Alberto Bissacco⁶, Leire Leache¹¹, Michele Tari¹², Salvatore Crisafulli⁷, Elisa Barbieri¹³, Luca Stona¹⁴, Xavier Garcia de Albeniz¹⁵, Satu Siiskonen¹⁶, Lamiae Grimaldi¹⁷, Tiago Vaz⁵, Rosa Gini^{4,2}, Olaf Klungel⁹, Elisa Martin Merino^{3,2}

¹Teamit Institute, Partnerships, Barcelona Health Hub, Barcelona, Spain. ²Vaccine monitoring Collaboration for Europe, Brussels, Belgium. ³Spanish Agency of Medicines and Medical Devices-AEMPS, Madrid, Spain. ⁴Agenzia Regionale di Sanita' Toscana, Florence, Italy. ⁵University Medical Center Utrecht, The Netherlands. ⁶Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain. ⁷University of Verona, Italy. ⁸PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands. ⁹Utrecht University, The Netherlands. ¹⁰Navarre Health Service, Pamplona, Spain. ¹¹Navarre Health Service, Spain. ¹²Caserta Local Health Unit, Caserta, Italy. ¹³University of Padua, Italy. ¹⁴Fondazione Penta ONLUS, Padova, Italy. ¹⁵RTI-Health Solutions, Barcelona, Spain. ¹⁶Utrecht Institute for Pharmaceutical Sciences, The Netherlands. ¹⁷l'Assistance Publique-Hôpitaux de Paris (APHP), University Paris-Saclay, Paris, France

Background. COVID-19 pandemic crowned the crucial role of real-world-evidence to promptly fuel researchers', national authorities', and regulators' preparedness for important and urgent healthcare decision-making processes, enriching society's awareness over the fundaments of decisions through solid communication based on big data.

Objectives. Calculation of effectiveness and waning of immunity of different COVID-19 primary vaccination (doses 1 and 2) and booster (dose 3) schemes with Comirnaty (PF), Spikevax (MD), and Vaxzevria (AZ) vaccines in preventing SARS-CoV-2 infection, hospitalization and death with COVID-19.

Methods. Study design: Matching 1:1 on the 2nd dose (primary scheme, adults: homologous vs heterologous; children: homologous vs unvaccinated) or 3rd dose (booster, adults: booster vs non-booster) vaccination date, dose 1 date and vaccine brand, vaccinees age, sex, geographical region, clinical history, and SARS-CoV-2 infection prior dose 1. Date of cohort entry: dose 2 (primary scheme) or dose 3 (booster) date. **Study Period:** December 2020 to December 2021/February 2022 (pre-Delta to Omicron). **Population:** 20 million adults and 300,000 children without prior SARS-CoV-2 infection. **Data sources:** 6 pan-European electronic healthcare data sources: IT: Caserta local health database (CASERTA), Societa Servizi Informatici (PEDIANET) database; ES: Spanish Pharmacoepidemiological Research Database for Public Health System (BIFAP), the Spanish Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària (SIDIAP) database; NL: PHARMO Database Network (PHARMO); UK: the British Clinical Practice Research Datalink (CPRD) Aurum. **Statistical Analyses:** Incidence rates (IR; 95% confidence intervals (CI)) and HR differences (95% CI) for each COVID-19 outcome. Inverse probability weighted (IPW) Cox proportional hazards regression (CI, 95%) to derive the average hazard ratio (HR) of COVID-19 outcomes. Adjusted % vaccine effectiveness (VE) (vaccinated vs comparator) = 1 minus the adjusted HR multiplied by 100 (corresponding CI calculated as 1-95%). Sensitivity analysis restricting to patients with prior testing for SARS-CoV-2 infection. **Covariates:** comorbidities, medication use, and health care utilization for at least 2 years prior the study period (2018-2020) as potential confounders for the IPW. **Reported Results:** VE (%) with statistical significance (otherwise specified).

Adults >17 years old
Homologous vs Heterologous Doses 1 and 2

SARS-CoV-2 infection

- Homologous doses 1 and 2 showed a slightly decreased VE compared to heterologous in BIFAP, SIDIAP and CASERTA
- The higher protection of heterologous doses 1 and 2 is mainly due to AZ dose 1
- BIFAP: decreased VE of homologous vs heterologous is more marked during the Delta than the Omicron period

Data source	Control person-days	Control cases	Control IR/100,000	Exposed person-days	Exposed cases	Exposed IR/100,000	Crude HR	LCI	UCI	HR adjusted	LCI	UCI	VE adjusted	LCI	UCI
BIFAP	3688819	1252	33.94	3654787	1659	45.39	1.36	1.26	1.46	1.36	1.27	1.47	-36%	-47%	-27%
SIDIAP	2819992	1113	39.47	2795362	1441	51.55	1.32	1.22	1.43	1.33	1.23	1.44	-33%	-44%	-23%
CASERTA	1025786	383	37.34	1019832	481	47.16	1.27	1.11	1.46	1.27	1.11	1.46	-27%	-46%	-11%

Hospitalization and Death with COVID-19

- No differences between homologous and heterologous doses 1-2 for hospitalization and <5 cases of deaths were found

Adolescents 12-17 years old
Homologous vs Heterologous Doses 1 and 2

SARS-CoV-2 infection

- Homologous vs heterologous doses 1 and 2 did not show differences

Hospitalization and Death with COVID-19

- No or <5 cases of hospitalization or deaths were found

Children and pre-adolescents 5-14 years old
Homologous Doses 1 and 2 vs Unvaccinated

SARS-CoV-2 infection

- PF vaccine was the most used brand. Delta: VE varied across data sources; Omicron: VE decreased in BIFAP.
- Children with prior SARS-CoV-2 infection: PF-MD did not avoid re-infection (vs unvaccinated).
- VE duration after dose 2: Delta: 4-5 months; Omicron: reverted to risk after 4 to 7 months (BIFAP)

Virus Variant	Data source	Control person-days	Control cases	Control IR/100,000	Exposed person-days	Exposed cases	Exposed IR/100,000	Crude HR	LCI	UCI	HR adjusted	LCI	UCI	VE adjusted	LCI	UCI
Delta	BIFAP	12995173	4347	33.45	13053027	3674	28.15	0.84	0.80	0.88	0.71	0.68	0.75	29%	25%	32%
	SIDIAP	5416515	2769	51.12	5463302	1546	28.30	0.55	0.52	0.58	0.51	0.48	0.54	49%	46%	52%
	PHARMO	1114853	865	77.59	1135644	203	17.88	0.23	0.20	0.26	0.23	0.19	0.26	77%	74%	81%
	CASERTA	815461	486	59.60	826263	200	24.21	0.40	0.34	0.47	0.40	0.34	0.47	60%	53%	66%
	PEDIANET	137156	64	46.66	138767	27	19.46	0.42	0.26	0.65	0.30	0.18	0.51	70%	49%	92%
Omicron	BIFAP	5266294	5290	100.45	5014004	8776	175.03	1.72	1.66	1.78	1.44	1.39	1.49	-44%	-49%	-39%
	INSPIRE	248731	728	292.69	257586	433	168.10	0.58	0.52	0.65	0.58	0.52	0.65	42%	35%	48%

Hospitalization and Death with COVID-19

- Hospitalization: in BIFAP, VE higher for Delta than Omicron. In SIDIAP, VE of 94% during Delta.
- Death: no or <5 cases

Adults >17 years old
3 doses (Boosted) vs 2 doses (Boosted)

SARS-CoV-2 infection

- Highest VE for PF (Italy) and MD (Italy, Netherlands) 3rd dose. VE of AZ 3 doses: 90% (CPRD).
- In Italy: homologous doses 1-2 and any 3rd dose showed higher VE for Omicron (70-73%) than Delta (66-65%) period. The opposite is observed with heterologous doses 1-2.
- In Spain: Delta, VE was 58-60%; Omicron, VE decreases to 19-36%, (19% in 3 homologous doses).
- VE of 3rd doses with heterologous doses 1-2 (AZ dose 1): 71% (INSPIRE, PF or MD 3rd dose), 41-58% in Spain (SIDIAP and BIFAP, respectively): PF: 63-34%, MD: 47-57%
- VE 3rd doses with homologous doses 1-2: 42-58% in Spain (Omicron: 36%) and Netherlands an 70% in Italy
- VE with homologous 3 doses: AZ, 90% (CPRD); PF, from 28% (BIFAP) to 69% (INSPIRE); MD from 41% (BIFAP) to 74% (PHARMO).

Data source	Control person-days	Control cases	Control IR/100,000	Exposed person-days	Exposed cases	Exposed IR/100,000	Crude HR	LCI	UCI	HR adjusted	LCI	UCI	VE adjusted	LCI	UCI	
Hospitalization with COVID-19																
Homologous 3 doses																
Overall	BIFAP	43269303	1547	3.58	43352456	528	1.22	0.34	0.31	0.38	0.33	0.3	0.36	67%	64%	70%
Overall	SIDIAP	8228666	364	4.42	8235337	145	1.76	0.4	0.33	0.48	0.39	0.32	0.47	61%	53%	68%
Overall	CASERTA	5444106	11	0.2	5444298	<5	0.04	0.18	0.04	0.82	0.2	0.04	0.9	80%	10%	96%
PF	BIFAP	36172189	1403	3.88	36247190	476	1.31	0.34	0.31	0.38	0.33	0.29	0.36	67%	64%	71%
PF	SIDIAP	6434452	314	4.88	6440421	118	1.83	0.38	0.3	0.46	0.36	0.29	0.45	64%	55%	71%
MD	BIFAP	7087035	144	2.03	7095187	52	0.73	0.36	0.26	0.5	0.35	0.26	0.49	65%	51%	74%
MD	SIDIAP	1791767	50	2.79	1792469	27	1.51	0.54	0.34	0.86	0.58	0.36	0.94	42%	6%	64%
Delta	BIFAP	26209211	831	3.17	26222885	276	1.05	0.33	0.29	0.38	0.32	0.28	0.37	68%	63%	72%
Delta	SIDIAP	8227633	364	4.42	8234304	145	1.76	0.4	0.33	0.48	0.39	0.32	0.47	61%	53%	68%
Omicron	BIFAP	17184114	734	4.27	17221221	256	1.49	0.35	0.3	0.4	0.33	0.29	0.38	67%	62%	71%
Omicron	CASERTA	2399442	10	0.42	2399592	<5	0.08	0.2	0.04	0.91	0.22	0.05	1	78%	0%	95%
Homologous doses 1-2 and Heterologous dose 3																
Overall	BIFAP	38599538	1039	2.69	38665590	257	0.66	0.25	0.22	0.28	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	0.21	0.17	0.27	79%	73%	83%
PF doses 1-2	BIFAP	22669955	609	2.69	22705886	153	0.67	0.25	0.21	0.3	0.26	0.22	0.31	74%	69%	78%
PF doses 1-2	SIDIAP	5640873	297	5.27	5645155	65	1.15	0.22	0.17	0.29	0.22	0.17	0.29	78%	71%	83%
MD doses 1-2	BIFAP	1850896	57	3.08	1845298	12	0.65	0.21	0.11	0.39	0.22	0.12	0.41	78%	59%	88%
AZ doses 1-2	BIFAP	14078687	373	2.65	14105706	92	0.65	0.25	0.2	0.31	0.24	0.19	0.31	76%	69%	81%
AZ doses 1-2	SIDIAP	3503991	101	2.88	3505169	19	0.54	0.19	0.12	0.31	0.19	0.11	0.31	76%	69%	89%
PF dose 3	BIFAP	8159498	247	3.03	8177489	59	0.72	0.24	0.18	0.32	0.24	0.18	0.32	76%	68%	82%
MD dose 3	BIFAP	30437969	792	2.6	30486030	198	0.65	0.25	0.21	0.29	0.25	0.22	0.3	75%	70%	78%
MD dose 3	SIDIAP	8994410	396	4.4	8999868	83	0.92	0.21	0.17	0.27	0.21	0.17	0.27	79%	73%	83%
Delta	BIFAP	13009885	370	2.84	13014173	84	0.65	0.23	0.18	0.29	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	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	0.26	0.22	0.31	74%	69%	78%
Death with COVID-19																
Homologous 3 doses																
Overall	BIFAP	43361621	675	1.56	43371503	189	0.44	0.28	0.24	0.33	0.26	0.22	0.31	74%	69%	78%
Overall	SIDIAP	8235852	156	1.89	8237787	33	0.4	0.21	0.15	0.31	0.2	0.14	0.3	80%	70%	86%
Overall	CPRD	19245486	26	0.14	19245639	6	0.03	0.23	0.09	0.56	0.23	0.1	0.57	77%	43%	90%
PF	BIFAP	36254930	622	1.72	36264044	182	0.5	0.29	0.25	0.35	0.28	0.23	0.33	72%	67%	77%
PF	SIDIAP	6440559	149	2.31	6442344	33	0.51	0.22	0.15	0.32	0.21	0.14	0.3	79%	70%	86%
PF	CPRD	19085685	25	0.13	19085838	6	0.03	0.24	0.1	0.59	0.24	0.1	0.59	76%	41%	90%
MD	BIFAP	7096612	53	0.75	7097380	7	0.1	0.13	0.06	0.29	0.12	0.05	0.26	88%	74%	95%
Delta	BIFAP	26221304	346	1.32	26225972	87	0.33	0.25	0.2	0.32	0.24	0.19	0.31	76%	69%	81%
Delta	SIDIAP	8234819	156	1.89	8236754	33	0.4	0.21	0.15	0.31	0.2	0.14	0.3	80%	70%	86%
Delta	CPRD	19234897	26	0.14	19235050	6	0.03	0.23	0.09	0.56	0.23	0.1	0.57	77%	43%	90%
Omicron	BIFAP	17270857	338	1.96	17274842	104	0.6	0.31	0.25	0.38	0.28	0.23	0.35	72%	65%	77%
Homologous doses 1-2 and Heterologous dose 3																
Overall	BIFAP	38670418	390	1.01	38676283	70	0.18	0.18	0.14	0.23	0.18	0.14	0.23	82%	77%	86%
Overall	SIDIAP	9192245	120	1.31	9193354	15	0.16	0.12	0.07	0.21	0.14	0.08	0.23	86%	77%	92%
PF doses 1-2	BIFAP	22707084	305	1.34	22711989	52	0.23	0.17	0.13	0.23	0.17	0.13	0.23	83%	77%	87%
PF doses 1-2	SIDIAP	5644657	112	1.98	5645665	14	0.25	0.12	0.07	0.22	0.13	0.08	0.24	87%	76%	92%
MD doses 1-2	BIFAP	1854938	18	0.97	1854938	5	0.27	0.28	0.1	0.75	0.3	0.11	0.8	70%	20%	89%
AZ doses 1-2	BIFAP	14108396	67	0.47	14109273	13	0.09	0.19	0.11	0.35	0.2	0.11	0.37	80%	63%	89%
PF dose 3	BIFAP	8179299	60	0.73	8179799	13	0.16	0.22	0.12	0.29	0.23	0.12	0.41	77%	59%	88%
MD dose 3	BIFAP	30489048	330	1.08	30494											