Executive Summary

P2-C3-002

A proof-of-concept vaccine effectiveness study in DARWIN EU®

Effectiveness of COVID-19 vaccines on severe COVID-19 and post-acute outcomes of SARS-CoV-2 infection

This Executive summary outlines the study design, data sources, analyses, results and lessons learned of this proof-of-concept vaccine effectiveness study in DARWIN EU. Detailed information is available in the study protocol and study report (EUPAS107615)

DARWIN EU	**Executive Summary for P2-C3-002**	
	Author(s): A. Jödicke, X. Li, M. Català Sabaté	**Date: 26/11/2024**
		Dissemination level: Public

Contents

RATIONALE

The present study was conducted as a proof-of-concept to inform the feasibility, study design, selection of fit-for-purpose data sources, and analytical approaches for COVID-19 vaccine effectiveness (VE) studies in DARWIN EU that would help to contribute to the totality of evidence on the benefit/risk profile of COVID-19 vaccines.

Study objectives

1. To assess the effectiveness of COVID-19 vaccination for the prevention of severe COVID-19 related outcomes (COVID-19 related hospitalisation or COVID-19 related death).
2. To assess waning of the effectiveness of COVID-19 vaccination for the prevention of severe COVID-19 related outcomes (COVID-19 related hospitalisation or COVID-19 related death).
3. To assess the effectiveness of COVID-19 vaccination for the prevention of all-cause mortality in the 3- and 6-months following discharge for COVID-19 related hospitalisation.
4. To assess the effectiveness of COVID-19 vaccination for the prevention of new-onset type 1 Diabetes Mellitus (DM1) in the 12 months after a SARS-CoV-2 infection.
5. To assess the effectiveness of COVID-19 vaccination for the prevention of new-onset type 2 Diabetes Mellitus (DM2) in the 12 months after a SARS-CoV-2 infection.
6. To assess the effectiveness of COVID-19 vaccination for the prevention of cardiovascular events in the 12 months after a SARS-CoV-2 infection.

METHODS

Retrospective population-level cohort study in the following data sources**:** CPRD GOLD (Clinical Practice Research Datalink - UK); IPCI (Integrated Primary Care Information Project - Netherlands); SIDIAP (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària - Spain).

Study Population

The study included individuals aged 12 years and older, with at least 365 days of prior data available in the data sources before their most recent COVID-19 vaccine dose, starting from December 2020.

Study Period

The study period differed based on the specific study objectives:

- Objectives 1-2: January 2022- 06/2023 (CPRD); March 2022 - 06/2023 (IPCI and SIDIAP)
- Objectives 3-6: January 2021 – June 2023 (all 3 data sources)

Exposure Definition

The definition of exposure varied according to the objectives:

- Objectives 1-2: The exposure was defined as the fourth vaccine dose. Comparisons were made between the fourth dose and three doses only.
- Objectives 3-6: Exposure was defined as receiving the second, third, or fourth vaccine dose. Comparisons were made between the second dose (versus one dose), the third dose (versus two doses), and the fourth dose (versus three doses).

Comparator Cohorts and Matching

Matching was used to minimise biases in estimating the vaccine effectiveness. Exposed individuals were paired through matching 1:1 with unexposed counterparts who had received one less vaccine dose at the time of matching. Matching used the variables age, sex, geographic location, immunocompromised status, previous vaccine brands, time from previous dose, previous SARS-CoV-2 diagnosis, history of conditions for prioritisation for vaccination, and a propensity score that was calculated using comorbidities and medication use in the 365 days before the index date (see definition below). We conducted the matching based on calendar week to account for changes in exposure status and community transmission rates over time. At the first day of each calendar week during the study period, we identified individuals who received an eligible vaccine dose during that week and matched to unexposed counterparts.

Index Date and Follow-Up

The index date for each matched pair was the date of the last dose received by the exposed individual. Follow-up began from this index date and continued until one of the following events: end of observation (censoring), receipt of the next vaccine dose (censoring), occurrence of the study outcome. If one subject in the matched pair was censored, follow-up for the pair ceased (this was not done if one counterpart experienced the study *outcome*).

Study Outcomes

The outcomes varied depending on the study objective:

- **Objectives 1-2**:
  - **COVID-19-related hospitalisation**: Defined as a hospital admission with a confirmed COVID-19 diagnosis or positive test result within a time window from 21 days before admission to three days after admission.
  - **COVID-19-related death**: Defined as a death with a confirmed COVID-19 diagnosis or positive test result within 28 days before death.
- **Objective 3**: **All-cause mortality** within a defined number of months following discharge from COVID-19 hospitalisation (within 3 months after discharge, and within 6 months after discharge).
- **Objective 4**: **Incidence of new-onset type 1 diabetes (DM1)**: Defined as the presence of a diagnostic code for DM1 between 30 and 365 days after a positive SARS-CoV-2 test or clinical diagnosis of COVID-19. This was limited to patients without a prior history of DM1, DM2, or any prior use of anti-diabetic medications.
- **Objective 5**: **Incidence of new-onset type 2 diabetes (DM2)**: Defined as the presence of a diagnostic code for DM2 or the first prescription of metformin between 30 and 365 days after a positive SARS-CoV-2 test or clinical diagnosis of COVID-19. This analysis was limited to patients without a history of DM1, DM2, or any prior use of anti-diabetic medications.
- **Objective 6**: **Incidence of cardiovascular events**: Defined as the presence of a diagnostic code for a selection of **cardiovascular events** occurring between 1 and 365 days after a positive SARS-CoV-2 test or clinical diagnosis of COVID-19. Details on selected diagnostic codes can be found in the full report.

Statistical Analyses

Hazards ratios (HR) were estimated using Cox proportional regression, conducted separately for each data source. The estimated HRs were transformed into VE estimates using the formula VE = 1-HR.

Results from the different data sources were pooled using random effect meta-analysis where appropriate and only if there were more than 2 data sources with available data for a given analysis (this is a standard approach in DARWIN EU studies, which in the case of this study meant data from all three data sources would need to be available). I^2 for heterogeneity was reported.

Results

The analyses were done in all three data sources apart from objective 3. Analysis of objective 3 was not conducted in CPRD GOLD because the lack of hospital data. The most common reason for censoring was the receipt of an additional vaccine dose.

Table 1 shows the results of the 4-dose vs 3-dose comparison for severe COVID-19 outcomes, and the various comparisons that were made for objectives 3-6. The follow-up periods are described with medians and ICR, which varied for each of the analyses and can be seen in Table 1. This should be considered when interpreting the effectiveness estimates.

Vaccine effectiveness against COVID-19 related **hospitalisation** of a fourth dose compared to only three doses was 26% (95% CI: 19% to 33%) and 46% (95% CI: 15% to 66%), in Spain (SIDIAP, with a median follow-up of 8 weeks) and Netherlands (IPCI, with a median follow-up of 21 weeks) respectively. This protection waned from 40% (95% CI: 30% to 49%) and 67% (95% CI: 19% to 86%) in the first four weeks of follow-up, to non-significant protection in weeks 21-24, with VE estimates of -22% (95% CI: -209% to 52%) and 67% (95% CI: -63% to 93%) in Spain (SIDIAP) and Netherlands (IPCI) respectively.

The effectiveness against COVID-19 related **death** of a fourth dose compared to only third doses was 30% (95% CI: 9% to 46%) in the meta-analysis. This protection waned from 73% (95% CI: -79% to 96%) in the first four weeks of follow-up, to 7% (95% CI:-130% to 63%) at the end of follow-up (weeks 25-28 after vaccination).

Effectiveness of a *third* dose against all-cause mortality in the months following discharge for COVID-19 related hospitalisation (objective 3) was 27% (95% CI: 20% to 34%) in the 3-month follow-up, and 25% (95% CI: 18% to 31%) in the 6-month follow-up compared to a *second* vaccine dose. These results are only available for the SIDIAP data source due to either the lack of hospital data linkage (CPRD) or very small event numbers (IPCI) in the other data sources.

Effectiveness of an additional vaccine dose against **new-onset type 1 diabetes** during the 30 to 365 days after a SARS-CoV-2 infection (objective 4) was not analysable due to very small numbers of new-onset type 1 diabetes in the exposure and comparator groups (below 5 events in all data sources).

Effectiveness of a *fourth* dose compared to a *third* dose against **new-onset type 2 diabetes** during the 30 to 365 days after a SARS-CoV-2 infection (objective 5) was non-significant: 23%, 95% CI -16% to 49% in the meta-analysis.

There was no clear conclusion regarding the effectiveness of an additional vaccine dose against **cardiovascular events** during the 1 to 365 days after a SARS-CoV-2 infection (objective 6). Results were inconsistent across data sources, with only one event (heart failure) being associated with a fourth dose in more than one data source, but not in the meta-analysis. Meta-analysis showed that effectiveness of a fourth dose compared to a third dose again major adverse cardiac events (MACE) during the 1st to 365 days after a SARS-CoV-2 infection was 23%, 95%CI 3% to 39%. Non-significant association being seen in meta-analyses of other cardiovascular events.

Table 1: Vaccine effectiveness against severe COVID-19 or post-acute sequelae of COVID-19

Outcome	Dose*	IPCI				CPRD GOLD				SIDIAP				VE meta-analyses
		N subjects	N events	Median FU (IQR)**	VE [95%CI]	N subjects	N events	Median FU (IQR)**	VE [95%CI]	N subjects	N events	Median FU (IQR)**	VE [95%CI]	VE [95%CI]
COVID-19 related hospitalisation	3rd dose	89,290	50	150 [22-239]	46% [15%; 66%]	Not possible because hospitalisation not available in this data source				295,169	914	56 [16-247]	26% [19%; 33%]	Not done (<3 data sources)
	4th dose	89,290	27							295,169	681			
COVID-19 related death	3rd dose	89,290	12	150 [22-239]	34% [-54%; 72%]	591,037	40	95 [16-207]	48% [14%; 69%]	295,169	223	56 [16-247]	23% [7%; 37%]	30% [9%; 46%]
	4th dose	89,290	8			591,037	21			295,169	174			
All-cause mortality following discharge from hospitalisation with COVID-19, 3 months	3rd dose	89,290	9	150 [22-239]	n.a. (<5 events)	Not possible because hospitalisation not available in this data source				295,169	186	56 [16-247]	36% [19%; 48%]	Not done (<3 data sources)
	4th dose	89,290	<5							295,169	121			
All-cause mortality following discharge from hospitalisation with COVID-19, 6 months	3rd dose	89,290	11	150 [22-239]	55% [-22%; 83%]	Not possible because hospitalisation not available in this data source				295,169	240	56 [16-247]	32% [18%; 44%]	Not done (<3 data sources)
	4th dose	89,290	5							295,169	165			
New-onset DM1	3rd dose	89,239	<5	150 [22-239]	n.a. (<5 events)	589,249	<5	95 [16-207]	n.a. (<5 events)	294,916	<5	56 [16-247]	n.a. (<5 events)	Not done (<3 data sources)
	4th dose	89,239	<5			589,249	<5			294,916	<5			
	2nd dose	129,704	<5	56 [12-277]	n.a. (<5 events)	484,961	<5	36 [11-327]	n.a. (<5 events)	921,190	<5	139 [19-366]	n.a. (<5 events)	Not done (<3 data sources)
	3rd dose	129,704	<5			484,961	<5			921,190	<5			
New-onset DM2	3rd dose	78,329	12	153 [23-240]	42% [-47%; 77%]	489,688	12	106 [17-208]	34% [-62%; 73%]	231,609	28	72 [17-247]	11 % [-49%;47%]	23% [-16%; 49%]
	4th dose	78,329	7			489,688	8			231,609	25			
	2nd dose	118,738	15	62 [12-290]	17% [-78%; 61%]	444,237	50	40 [12-336]	13% [-29%; 42%]	809,703	188	171 [20-379]	-8% [-30%;11%]	-2% [-22%; 14%]
	3rd dose	118,738	12			444,237	44			809,703	204			
Acute myocardial infarction	3rd dose	88,705	14	149 [22-239]	36% [-47%; 72%]	588,026	11	95 [16-207]	19% [-95%; 66%]	293,297	62	56 [16-247]	19% [-17%-44%]	22% [-8%; 43%]
	4th dose	88,705	9			588,026	9			293,297	51			
Angina broad	3rd dose	88,588	18	149 [22-239]	12% [-70%; 54%]	581,363	42	93 [16-206]	4% [-47%; 37%]	286,693	187	56 [16-247]	-1% [-24%; 17%]	0.0% [-19%; 16%]
	4th dose	88,588	16			581,363	41			286,693	192			
Angina narrow	3rd dose	88,588	18	149 [22-239]	12% [-70%; 54%]	589,237	8	95 [16-207]	26% [-113%; 74%]	293,282	44	56 [16-247]	15% [-30%; 44%]	15% [-20%; 40%]
	4th dose	88,588	16			589,237	6			293,282	38			
Arterial thromboembolism	3rd dose	88,491	16	149 [22-239]	32% [-47%; 68%]	587,409	12	95 [16-207]	-7% [-134%; 51%]	289,922	171	56 [16-247]	13% [-8%; 30%]	13% [-7; 29%]
	4th dose	88,491	11			587,409	13			289,922	151			
Cerebrovascular disorders	3rd dose	88,313	17	149 [22-239]	24% [-56%; 63%]	587,908	8	95 [16-207]	-23% [-211%; 51%]	289,844	163	56 [16-247]	12% [-10%; 29%]	12% [-9; 28%]
	4th dose	88,313	13			587,908	10			289,844	145			
Heart failure	3rd dose	88,283	37	149 [22-239]	30% [-13%; 57%]	587,431	22	95 [16-207]	60% [14%; 81%]	285,443	475	56 [16-246]	15% [3%; 25%]	27% [-2; 48%]
	4th dose	88,283	26			587,431	9			285,443	411			
Mace	3rd dose	87,607	48	148 [22-239]	34% [-2%; 57%]	584,340	39	95 [16-207]	39% [0.0%; 63%]	282,931	593	56 [16-246]	14% [3%; 23%]	23% [3; 39%]
	4th dose	87,607	32			584,340	24			282,931	518			

*: All information presented in this table represented the matched cohort. For example, in the first two rows, "3rd dose" in the first panel refers to the 3rd dose cohort matched to the 4th dose, and follow-up time started at the index date of the pair (vaccine date of the 4th dose) .

**Median follow-up for the exposed group. FU: Follow-up, IQR: Interquartile range.

DISCUSSION

This proof-of-concept vaccine effectiveness study in DARWIN EU® reports that a fourth vaccine dose provided additional protection against severe COVID-19, on top of remaining protection provided by previous vaccine doses. When our estimates of the fourth dose VE against COVID-19 related hospitalisation and death is compared to results from previous studies, a smaller effect size is observed in the present study. This could be in part due to differential uptake of booster vaccines and different levels and strains of SARS-CoV-2 circulating across data sources and study periods in our study compared to previous studies. In addition, evidence from this study cannot be fully contextualised with other studies, due to differences in study designs, follow-up periods used, and different vaccination schedules in the countries where the data sources are located. It is important to consider that such characteristics may vary substantially across studies. While we planned to look into different vaccine variants (monovalent, bivalent), this information was only available in one of the participating data sources, i.e. IPCI While the present study included any fourth dose with no age restriction in the study population, a study in the Nordic countries [1] included recipients of bivalent vaccine over 50 years of age. A Norwegian study among individuals aged ≥75 years who received at least 3 doses of COVID-19 vaccines showed that, compared to having received a third dose > 24 weeks before the fourth dose, receiving a fourth dose was associated with reduced risk for COVID-19-associated mortality during the 2 to 9 weeks after vaccination. Whiles the original publication reported hazard ratios, we calculated the vaccine effectiveness using formula of 1 – HR: BA.1 (VE 92% [68 to 98]), BA.4–5 (VE 73% [44 to 86]) and a monovalent dose (VE 66% [55% to 74]). This study also found that the protective effect of the fourth dose waned over time, and no additional protective effect was observed after 33 weeks, which corroborates our results [2]. Finally, the pooled analyses performed by the ECDC in six European countries/regions (BE, DK, LU, ES/Navarra, NO, PT) mainly compared VE of the fourth dose to primary vaccination (the combination of dose 1 and 2 in the case of mRNA vaccines), which could be one reason why 'higher' VE estimates were obtained [3].

LESSONS LEARNED

This proof-of-concept study on the effectiveness of additional COVID-19 vaccination doses to prevent *severe* health outcomes related to COVID-19 and post-acute outcomes of COVID-19 infection has generated important insights regarding the feasibility, set-up, and analysis of VE studies in DARWIN EU.

Feasibility

The study successfully demonstrated that large-scale, retrospective studies on COVID-19 VE are feasible using diverse data sources across multiple countries. The collaborative effort using CPRD, IPCI, and SIDIAP data sources confirmed the capability of conducting multi-data source VE studies in DARWIN EU, even if limited in terms of number and possibilities.

Study Design

The study utilised a combination of exact matching and large-scale propensity score matching. Although this may result in smaller matched cohorts, matching exposed and unexposed individuals on a variety of relevant factors is essential to reduce biases.

Several learnings emerged during the analytical process:

- Immune Response Window: the *immune response window* are the first 7-14 days after vaccination during which immunity is being developed by the immune system (other estimates such as 10 days are also occasionally used). This is a form of *delayed treatment effect*. When the index date is set as the date of the last vaccine dose and follow-up is started at index date, individuals who develop outcomes during the *immune response window* will be misclassified as "vaccine failures". This misclassification could lead to an underestimation of vaccine efficacy and contribute to Proportional hazards assumption (PHA) violation (see section below on Proportional hazards assumption). Follow up could start a certain number of days after the last vaccine dose (a number based on recent literature) to account for the time needed for the immune response to develop.
- Weekly matching and follow-up: weekly matching was used to align exposed and unexposed participants on follow-up time. If one person in a matched pair was censored (in the majority of cases due to receiving an additional vaccine dose), the entire pair was censored. The combination of these two inadvertently contributed to shorter follow-up periods at risk. For example, if an exposed person was matched with an unexposed individual in week 0, and the unexposed person received a vaccine dose in week 1, both would be censored after just one week. This limitation makes it difficult to assess long-term effectiveness. In future studies, the impact of this phenomenon could be assessed, and illustrated using survival curves that depict the time to censoring caused by the vaccination of the matched counterpart.

Statistical analysis

- Cohort diagnostics: It was shown to be important to analyse the impact of exclusion criteria on cohort sample size before the effectiveness analyses are conducted. This early analysis can reveal potential issues, as was seen with SIDIAP, where the accepted window for a second vaccine dose needed to be extended to reflect local vaccination practice.
- Proportional hazards assumption (PHA): a Cox proportional regression model was used to estimate the hazard ratio (HR) to then estimate vaccine effectiveness as 1-HR. An important assumption of the Cox regression model is that the HR is constant over time (the *proportional hazards* assumption, PHA). In this study, violations of the PHA were observed, largely due to the delayed treatment effect (see above), and vaccine waning (while protection against severe outcomes was strongest shortly after vaccination, it decreased as time progressed). The report therefore includes alternative estimates of vaccine effectiveness based on other summary measures such as incidence rate ratios. To address PHA violation, future studies could:
    - Start follow-up after the *immune response window* has passed (see above).
    - Explore landmarking in Cox regression if PHA violation occurs before considering other summary measures and statistical models not relying on the proportional hazard assumption.
- Consistent follow-up across data sources; To facilitate interpretation of VE results, the follow-up period could be cut-off when it reaches a meaningful period (such as 3 or 4 months), and each data source could have the same cut-off to ease interpretation. This could also allow for VE estimates to be given for the period in question, rather than for a "median follow-up of x months".
- Cross-country differences: While the use of a common data model facilitated federated analyses, it is important to account for variations in healthcare guidelines and vaccination practices between countries. For instance, country-specific vaccination schedules should be considered when identifying individuals who received the primary vaccine series.

Meta-analysis

Although combining results from multiple data sources through meta-analysis worked well for some objectives, it was challenging in situations when event numbers were low, when results were inconsistent across data sources , and when follow-up periods were not similar between analyses (see above). These sources of heterogeneity may complicate the interpretation of the results from meta-analysis.

Limited data counts for some outcomes

Post-acute complications of COVID-19 infection including new onset diabetes and cardiovascular and thromboembolic events were rare. This was likely due to a limited duration of follow-up (see above), but also the protective effect from previous vaccine doses. The small number of events during follow-up led to a lack of power and resulting wide confidence intervals in effect estimates, underscoring the need for longer follow-up and/or larger study populations to obtain more precise estimates. In addition, it should be considered whether this is related to data quality issues (these outcomes may be recorded in the data sources with some delay, which could have a negative impact especially considering the short at-risk periods, or not be captured).

Communicating results

Effective communication of study results is key. Time-to-event curves are particularly useful in illustrating the findings and trends over time, helping in the interpretation of VE results across different time points.

CONCLUSION

The lessons learned from this proof-of-concept study can inform the design and implementation of future VE studies in DARWIN EU, potentially extending beyond COVID-19 vaccination to other vaccines. The VE findings from this study also add to the growing body of evidence on the protective benefits of COVID-19 vaccines.

DISCLAIMER

The study received support from the European Medicines Agency, this report expresses the opinion of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

KEY REFERENCES

[1] Andersson NW, Thiesson EM, Baum U, Pihlström N, Starrfelt J, Faksová K et al. Comparative effectiveness of bivalent BA.4-5 and BA.1 mRNA booster vaccines among adults aged ≥50 years in Nordic countries: nationwide cohort study. BMJ. 2023 Jul 25;382:e075286. doi: 10.1136/bmj-2022-075286.

[2] Stecher M, Brathen Kristoffersen A, Lie K, et al. Effectiveness and durability of a second COVID-19 booster against severe outcomes among older people in Norway: a population-based cohort study comparing mono- and bivalent booster doses. *International Journal of Epidemiology* 2023;52:1716–24. doi: https://doi.org/10.1093/ije/dyad114

[3] ECDC TECHNICAL REPORT. Interim analysis of COVID-19 vaccine effectiveness against hospitalisation and death using electronic health records in six European countries November 2023 [Available from: https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-vaccine-effectiveness-hospitalisation.pdf.