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Vaccine effectiveness of JCOVDEN single-dose against COVID-19 hospitalisation in Europe: An id.DRIVE test-negative case-control study

Chloé Wyndham-Thomas [a], E. Claire Newbern [b], Ainara Mira-Iglesias [c,d,e], Akshat Dwivedi [a], Alejandro Orrico Sánchez [c,d,e], Andrés Antón [f], Charlotte Martin [g], Giancarlo Icardi [h], Irma Casas [i], Kok Yew Ngew [a], Laura Drikite [a], Leonie de Munter [a], Gerrit Luit ten Kate [j], Nikki Vroom [a], Sebastian Baumgartner [k], Susana Otero-Romero [f], Xavier Holemans [l], Kaatje Bollaerts [a], Nicolas Praet [b,m,*]

[a] P95 Clinical and Epidemiology Services, Diestsevest 125, Leuven 3000, Belgium
[b] Janssen Research & Development, LLC, 200 Tournament Dr, Horsham, PA 19044, United States
[c] Valencia Hospital Network for the Study of Infectious Diseases, Fundación Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana, Av. de Catalunya 21, Valencia 46020, Spain
[d] Vaccine Research Department of Fisabio-Public Health, Valencia, Spain
[e] CIBER de Epidemiología y Salud Pública, Instituto de Salud Carlos III, Madrid, Spain
[f] Hospital Universitari Vall d'Hebron, Paseo Vall d'Hebron 119-129, Barcelona 08035, Spain
[g] Le Centre Hospitalier Universitaire St Pierre, Rue Haute 322, Brussels 1000, Belgium
[h] Centro Interuniversitario per la Ricerca sull'Influenza e le altre Infezioni Trasmissibili Largo R. Benzi 10, Genoa 16132, Italy
[i] Hospital Universitari Germans Trias i Pujol, Carretera del Canyet, Badalona, Barcelona 08916, Spain
[j] Universitair Ziekenhuis Antwerpen, Drie Eikenstraat 655, Edegem 2650, Belgium
[k] Klinik Favoriten, Kundratstraße 3, Wien 1100, Austria
[l] Grand Hôpital de Charleroi, Grand Rue 3, Charleroi B-6000, Belgium
[m] Janssen Research & Development, LLC, 2340, Turnhoutseweg 30, Beerse 2340, Belgium

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ABSTRACT

Background: JCOVDEN (Ad26.COV2.S), a viral-vector vaccine, was granted conditional marketing authorisation in the European Union for the prevention of COVID-19 in early 2021. We present JCOVDEN single-dose vaccine effectiveness (VE) estimates against COVID-19 hospitalisation.
Methods: The id.DRIVE (previously COVIDRIVE) COVID-19 VE study is an ongoing European non-interventional, multi-centre study with a test-negative case-control design. Study participants were adults ≥ 18 years old, hospitalised with severe acute respiratory infection between 1 May 2021 and 28 February 2023. Estimated as a single measure over the entire study period, VE was stratified by risk group, time since vaccination intervals (14 days-12 weeks, 12-to-25 weeks, 25-to-52 weeks, > 52 weeks), SARS-CoV-2 variant and calendar time categories. All estimates were adjusted for symptom-onset date, age, sex, and number of pre-defined chronic conditions.
Results: Overall, VE was 55.6 % (95 % CI 23.6; 74.2) for a median time since vaccination of 146 days. For 18- to 49-year-olds, VE was 61.6 % (95 % CI 16.2; 82.4), 57.7 % (95 % CI 3.4; 81.5) for 50- to-64-years-olds, and 40.8 % (95 % CI −6.0; 66.9) for ≥ 65-year-olds. Most precise estimates were obtained for time since vaccination 12-

Abbreviations: AUC, area under the curve; CHU, Centre Hospitalier Universitaire; CI, confidence interval; CIRI-IT, Centro Interuniversitario per la Ricerca sull'Influenza e le altre Infezioni Trasmissibili; COVID-19, coronavirus disease 2019; ECDC, European Centre for Disease Prevention and Control; ECRF, electronic case report; EMA, European Medicines Agency; EU, European Union; GAM, Generalised additive model; GEE, generalised estimating equations; GHdC, Grand Hôpital de Charleroi; GISAID, Global Initiative on Sharing All Influenza Data; GTPUH, Hospital Universitari Germans Trias i Pujol; HCW, healthcare worker; HMA, Heads of Medicines Agencies; HUVH, Hospital Universitari Vall d'Hebron; ICC, interclass correlation coefficient; ICU, intensive care unit; IEC, independent ethics committee; IQR, interquartile range; IRCCS, Istituto di Ricovero e Cura a Carattere Scientifico; JCOVDEN, previously COVID-19 Vaccine Janssen; N/N, number; NA, not applicable; NE, not estimable; OR, odds ratio; PPP, public-private partnership; RNA, ribonucleic acid; RT-PCR, reverse transcription polymerase chain reaction; SARI, severe acute respiratory infection; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNCC, test-negative case-control; TTS, thrombocytopenia syndrome; UZA, Universitair Ziekenhuis Antwerpen; VAHNSI, Valencia Hospital Network for the Study of Infectious Diseases; VE, vaccine effectiveness; WHO, World Health Organization

* Corresponding author at: Janssen Research & Development, LLC, 2340, Turnhoutseweg 30, Beerse 2340, Belgium.
E-mail address: npraet@its.jnj.com (N. Praet).

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to- 25-week interval (59.2 % [95 % CI 25.0; 77.8]) and for the calendar time period 1 Aug 2021 –30 Nov 2021 (Delta predominant; 51.2 % [95 % CI 21.7; 69.6]).
Conclusion: The JCOVDEN single-dose protected against COVID-19 hospitalisation. It is effective for at least six months, with VE estimates comparatively lower in the older age groups. Results had low to medium levels of certainty and are to be interpreted with caution.

Introduction

Vaccines have played a pivotal role in the response to the coronavirus disease 2019 (COVID-19) pandemic, having saved at least 1.4 million lives in Europe, according to the World Health Organization (WHO) [1]. The JCOVDEN vaccine (previously COVID-19 Vaccine Janssen; Ad26.COV2.S) is a replication-incompetent viral-vector vaccine that uses a recombinant adenovirus type 26 to encode the spike glycoprotein of the 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2). Based on favourable efficacy and safety data [2], JCOVDEN was granted a conditional marketing authorisation in the European Union (EU) for the prevention of COVID-19 on 11 March 2021, with conversion to a standard marketing authorisation on 9 January 2023 [3]. The vaccine was authorised for adults 18 years and older, initially as a single-dose priming schedule and, from December 2021, also as a booster dose.

JCOVDEN became available across the EU in April 2021, approximately four months into the national COVID-19 vaccine campaigns, broadening vaccines options. Through November 2022, the vaccine was administered mainly for priming and only rarely as a booster dose, following evolving country-specific recommendations (Table 1) [4]. The identification of thrombosis with thrombocytopenia syndrome (TTS) as a very rare adverse event of COVID-19 viral-vector vaccines by post-marketing surveillance led several EU countries to interrupt their use and/or set a minimum age for use [5].

Similar to vaccine safety monitoring, continuous vaccine effectiveness (VE) monitoring is essential for evaluating the benefit-risk profile of vaccines. Post-marketing VE studies provide real-world evidence complementary to the data generated by clinical trials [6]. In particular, these studies provide VE estimates for the broader population, including individuals often excluded from clinical trials (e.g., those with severe chronic conditions and older adults). They also assess the effects of circulating variants and monitor for potential waning of protection. COVID-19 VE monitoring in Europe has been ensured by dedicated studies of the public-private partnership (PPP) COVIDRIVE, a unique consortium of pharmaceutical companies, public health institutes and research groups. This PPP has now evolved to id.DRIVE, having broadened its scope beyond SARS-CoV-2 (https://iddrive.eu/).

Here, we present the main results of id.DRIVE's JCOVDEN study, evaluating the vaccine's VE against COVID-19 severe acute respiratory infection (SARI) hospitalisation over 22 months, including seasons dominated by Delta and Omicron variants. We further describe the strengths, complexities and challenges faced in the design and conduct of this study, highlighting lessons learnt for future (pandemic) VE studies.

Methods

Study objectives

The primary objective of this study was to estimate the VE of JCOVDEN single-dose primary series against COVID-19 hospitalisation due to laboratory-confirmed SARS-CoV-2 in adult SARI patients. Per secondary and exploratory objectives, results were stratified by age, time since vaccination intervals, SARS-CoV-2 genetic variant, calendar time categories (as variant-proxy), and presence of studied chronic conditions, including immunodeficiency. In addition, several sensitivity analyses were performed to test the robustness of the primary objective. Finally, the complexities and challenges faced in the design and conduct of this study were compiled and discussed to provide lessons learnt for future studies.

Study design and setting

The master id.DRIVE COVID-19 VE study (EUPAS42328) is an ongoing non-interventional, multi-centric, test-negative case-control (TNCC) study producing brand-specific VE estimates against COVID-19 hospitalisation as part of post-authorisation regulatory commitments in Europe, as previously described [7]. This publication reports the results of the id.DRIVE JCOVDEN-specific study (VAC31518COV4004) that included data collected between 1 May 2021 and 28 February 2023. The study included eight Study Contributors (Table 2), participating sites that are either hospitals or hospital networks, distributed across four European countries, i.e., Austria, Belgium, Italy, and Spain.

Study participants

The study population included adults 18 years and older who were hospitalised with SARI for at least an overnight stay. SARI was defined as a hospitalised person with suspicion of respiratory infection with onset within the last 14 days prior to hospital admission of at least one of the following symptoms: cough, fever, shortness of breath, or sudden onset of anosmia, ageusia or dysgeusia, (adapted from the European Centre for Disease Prevention and Control [ECDC] case-definition) [8]. SARI patients were identified either prospectively (e.g., during consultation in the emergency department or at admission to infectious disease or internal medicine ward) or retrospectively (by hospital database search or from positive respiratory specimens laboratory-confirmed at the virology laboratory). To be included in this analysis, SARI patients must have been eligible for COVID-19 vaccination following the immunisation recommendations in the country of care-seeking and had either never received a COVID-19 vaccine ('unvaccinated') or had been vaccinated with a single dose of JCOVDEN as primary series, without any subsequent booster dose. Patients who had a COVID-19 hospitalisation within three months prior to the current admission, who could not be swabbed, who had a recent vaccination (vaccinated with JCOVDEN < 14 days prior to SARI symptom-onset), or who were vaccinated with other vaccine brands were excluded from the analysis.

Laboratory testing

Respiratory specimens were collected and tested as per routine clinical practice. While nasopharyngeal or oropharyngeal swabs were recommended in the protocol, other types of respiratory specimens were also accepted. Specimens accepted for the study were those collected between 14 days prior to and up to 24 hours after arrival at the hospital and tested for SARS-CoV-2 by reverse

Table 1
National COVID-19 immunisation recommendations and national vaccine coverage estimates in adults ≥ 18 years for JCOVDEN, at start and end of the study period.
Source: https://www.ecdc.europa.eu/en/publications-data/covid-19-vaccine-tracker.

Country	Date and summary of JCOVDEN recommendations as primary schedule[a]	National vaccine coverage, first dose				National vaccine coverage, first additional dose			
		Any COVID-19 vaccine		JCOVDEN		Any COVID-19 vaccine		JCOVDEN	
		Week 18 2021[b]	Week 9 2023[c]	Week 18 2021[b]	Week 9 2023[c]	Week 18 2021[b]	Week 9 2023[c]	Week 18 2021[b]	Week 9 2023[c]
Austria[d]	23 March 2021: Recommended for all 18-year-olds and older, except pregnant women December 2022: Vaccine no longer used	37.2 %	86.3 %	0.1 %	4.9 %	NA	70.3 %	NA	0.2 %
Belgium	28 April 2021: recommended for all 18-year-olds and older 26 May 2021: recommended only for 41-year-olds and older 09 June 2021: opened to 18–40-year-olds on voluntary basis	39.5 %	90.9 %	0.3 %	4.6 %	NA	76.7 %	NA	0.0 %
Italy	18 April 2021: preferably in 60-year-olds and older and people at risk 07 February 2023: Vaccine is no longer used	33.8 %	92.7 %	0.4 %	3.0 %	NA	86.2 %	NA	0.0 %
Spain	22 April 2021: recommended for 70- to 79-year-olds and in specific groups of adults aged 18 years and older (e.g. those residing in remote areas, in congregate settings or unhoused) 12 May 2021: 50–59-year-olds and those classified as vulnerable (all ages) 02 June 2021: extended to 40–49-year-olds	35.5 %	93.1 %	0.5 %	5.1 %	NA	67.6 %	NA	0.0 %

Abbreviations: NA, not applicable, additional dose not yet implemented at start of study period.
[a] Obtained from official external sources, despite authorisation of JCOVDEN as an additional dose by the EMA on 15 December 2021, no specific national recommendations for the use of JCOVDEN as an additional dose were identified.
[b] Week 18 2021 starts 6 May 2021.
[c] Week 9 2023 starts 23 February 2023.
[d] Only general (not time-specific) country information was available for Austria.

transcription polymerase chain reaction (RT-PCR) or another RNA amplification system with equivalent sensitivity (e.g., transcription-mediated amplification). Those with laboratory-confirmed SARS-CoV-2 infection were cases, whereas those with a negative laboratory test result were controls. Prospectively collected SARS-CoV-2 positive samples were genotyped using either whole genome sequencing or next-generation sequencing classified according to the Pangolin nomenclature [9].

Study variables

Key covariates collected included age at the time of hospitalisation admission, sex, and chronic conditions associated with a higher risk of severe SARS-CoV-2 (asthma, lung disease, cardiovascular disease, hypertension, chronic kidney disease, chronic liver disease, type 2 diabetes, cancer, and immunodeficiency). Chronic conditions were ongoing at the time of hospitalisation, except for cancer that was either in treatment, in active follow-up, or within 5 years since post-curative treatment. Other descriptive variables collected were long-term care facility residence, healthcare worker (HCW), pregnancy, body mass index, smoking history, previous SARS-CoV-2 infection (laboratory-confirmed or clinical diagnosis specified), viral respiratory co-infection, anti-pneumococcal and influenza vaccination status, SARS-CoV-2 prophylactic and therapeutic medicines received, and length of hospital stay. Admission to the intensive care unit (ICU) and/or in-hospital death during SARI hospitalisation were recorded to calculate in-hospital progression risks (proportion of ICU and in-hospital deaths among all test-positive cases, proportion of deceased among those admitted to ICU).

Data sources and data management

Data sources included hospital and general practitioner medical records, laboratory records, vaccination registries (national or regional), and/or vaccination cards. An electronic case report (eCRF) form was developed to standardise data collection across Study Contributor sites. The Castor® eCRF software was used for data capture and monitoring. Only pseudonymised data was transferred from the Study Contributors to the id.DRIVE research server, a dedicated, secured central server hosted by P95. All data processing activities done in id.DRIVE are in line with the General Data Protection Regulation [10].

Statistical methods

COVID-19 VE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients was estimated over the entire 22-month long study period, then stratified by age groups (18- to 49-year-olds, 50-to-64-years-olds, ≥65-year-olds), time since vaccination intervals (14 days-12 weeks, 12-to-25 weeks, 25- to-52 weeks, > 52 weeks), chronic conditions (none or ≥1 of the chronic conditions captured by the eCRF), SARS-CoV-2 variant by sequencing (Delta, Omicron [all subvariants], Omicron BA.1), and calendar time categories of symptom-onset as proxy for viral variant (1 May 2021 to 31 July 2021 [Gamma, Beta, Alpha, Delta co-circulation], 1 August 2021 to 30 November 2021 [Delta predominant], 1 December 2021 to 31 December 2021 [Delta, Omicron BA.1 co-circulation], 1 January 2022 to 30 April 2022 [Omicron BA.1, BA.2 co-circulation], 1 May 2022 to 30 June 2022 [Omicron BA.2, BA.4, BA.5 co-circulation], 1 July 2022 to 30 September 2022 [Omicron BA.5 predominant], 1 October 2022 to 28 February 2023 [Omicron BA.5, BQ.1, BA.2.7, XBB co-circulation]). These categories of the calendar time were defined such that the intervals coincided with changes in circulating SARS-CoV-2 strains as reported by ECDC (erviss.org) and Global Initiative on Sharing All Influenza Data (GISAID; covariants.org).

Table 2
Overview of Study Contributors participating in the id.DRIVE COVID-19 vaccine effectiveness study.

Country	Study Contributor	Hospital	Subject recruitment	Site activation date[a]	Start date of retrospective data collection[b]
Austria	Klinik Favoriten	Klinik Favoriten	Prospective and retrospective	4 April 2022	1 June 2021
Belgium	Le Centre Hospitalier Universitaire St. Pierre	Le Centre Hospitalier Universitaire St. Pierre	Prospective and retrospective	3 February 2022	1 June 2021
	Universitair Ziekenhuis Antwerpen	Universitair Ziekenhuis Antwerpen	Prospective and retrospective	28 December 2021	1 June 2021
	Grand Hôpital de Charleroi	Grand Hôpital de Charleroi	Retrospective	NA	1 May 2021
Italy	Centro Interuniversitario per la Ricerca sull'Influenza e le altre Infezioni Trasmissibili	Hospital 1: IRCCS Ospedale Policlinico San Martino, Genoa Hospital 2: Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan Hospital 3: Azienda Ospedaliero-Universitaria Sant'Andrea, Rome Hospital 4: Azienda Ospedaliero Bari Hospital	Prospective	16 November 2021	NA
Spain	Valencia Hospital Network for the Study of Infectious Diseases	Hospital 1: Hospital General Castellon Hospital 2: Hospital La Fe Hospital 3: Hospital Dr. Peset Hospital 4: Hospital Marina Baixa	Prospective	8 September 2021	NA
	Hospital Universitari Germans Trias I Pujol	Hospital Universitari Germans Trias I Pujol	Prospective and retrospective	20 October 2021	1 June 2021
	Hospital Universitari Vall d'Hebron	Hospital Universitari Vall d'Hebron	Prospective and retrospective	14 February 2022	30 October 2021

Abbreviations: NA, not applicable– no retrospective recruitment; IRCCS, Istituto di Ricovero e Cura a Carattere Scientifico.
[a] Date the site opened for recruitment. For all sites except Grand Hôpital de Charleroi (only retrospective data), a maximum of 8 days was recorded between site activation date and first prospectively enrolled patient
[b] Date of hospital admission of the first admitted patient among the retrospective data.

We calculated VE as (1-*OR*) x 100 %, where OR denoted the adjusted exposure odds ratio, comparing the odds of vaccination among SARS-CoV-2 test-positive cases to the odds of vaccination among SARS-CoV-2 test-negative controls. Estimates were obtained using generalised estimating equations (GEE), used to produce population-averaged estimates from the pooled dataset that combined individual-level pseudonymised data from Study Contributors [11–13]. All estimates were confounder-adjusted, meaning adjusted for symptom-onset date, age, sex, and number of chronic conditions as per id.DRIVE COVID-19 VE study master protocol. Missing data was handled by performing a complete case analysis for case/control status, symptom-onset date, vaccination status, Study Contributor, sex, age, and reported chronic conditions. The effects of symptom-onset date and age were modelled using penalised cubic regression splines. As a secondary analysis, generalised additive models (GAM) with Study Contributor included as an additional covariate were used as an alternative to GEE [14]. In addition, an alternative summary measure of VE was obtained by calculating the area under the curve (AUC) of the spline-based VE estimates up to 6 months, by considering time since vaccination as the continuous exposure variable instead of a binary exposure variable.

For sensitivity analyses, the primary objective was re-analysed using GEE, by (i) restricting the accepted time between symptom-onset and swab to ≤ 3 days, (ii) extending the maximum time between hospital admission and swab from 24 hours to 72 hours, (iii) using the WHO SARI case-definition (acute respiratory infection with symptom-onset within the last 10 days prior to hospital admission, with a history of measured fever or measured fever of ≥38 C° *and* cough) [15], and (iv) including only prospectively enrolled study participants.

All data transformations and statistical analyses were conducted using the statistical programming environment R (version 4.1.2). To ensure the reproducibility of the analysis, the R package *renv* was used (https://rstudio.github.io/renv/articles/renv.html).

Protocol, ethical approvals and informed consent

The id.DRIVE COVID-19 VE study is conducted based on a master protocol that was approved by the relevant independent ethics committees (IECs) following local regulations and the Declaration of Helsinki. The master protocol was harmonised to the extent possible with the ECDC/WHO-EU protocol and registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. The latest version of the master protocol can be found in the Heads of Medicines Agencies - European Medicines Agency (HMA-EMA) catalogue of real-world data studies (EUPAS42328).

Informed consent was provided either by the participant or the participant's Legally Acceptable Representative(s). Waiver of informed consent was authorised by the IECs of Germans Trias i Pujol and Vall d'Hebron Hospitals, as the study activities (laboratory testing and information collected) were part of the routine clinical practice and epidemiological surveillance. Waiver of consent for retrospective data was also approved for all sites participating in retrospective data collection, except for Grand Hôpital de Charleroi (GHdC), which used an opt-out information letter sent to all eligible and non-deceased subjects.

Results

Participants characteristics

Of the 8752 patients hospitalised with SARI and recruited in id.DRIVE from 1 May 2021 to 28 February 2023, 1318 were included in JCOVDEN-specific analysis: 997 test-positive cases (COVID-19 cases) and 321 test-negative controls. The number of patients excluded and the reason for exclusion are presented in Fig. 1. Additionally, Fig. 2 shows the number of SARI patients included according to calendar week of symptom-onset and SARS-CoV-2 test status a) overall and b) by type of enrolment (prospective and retrospective). Most SARI patients included in the study had symptom

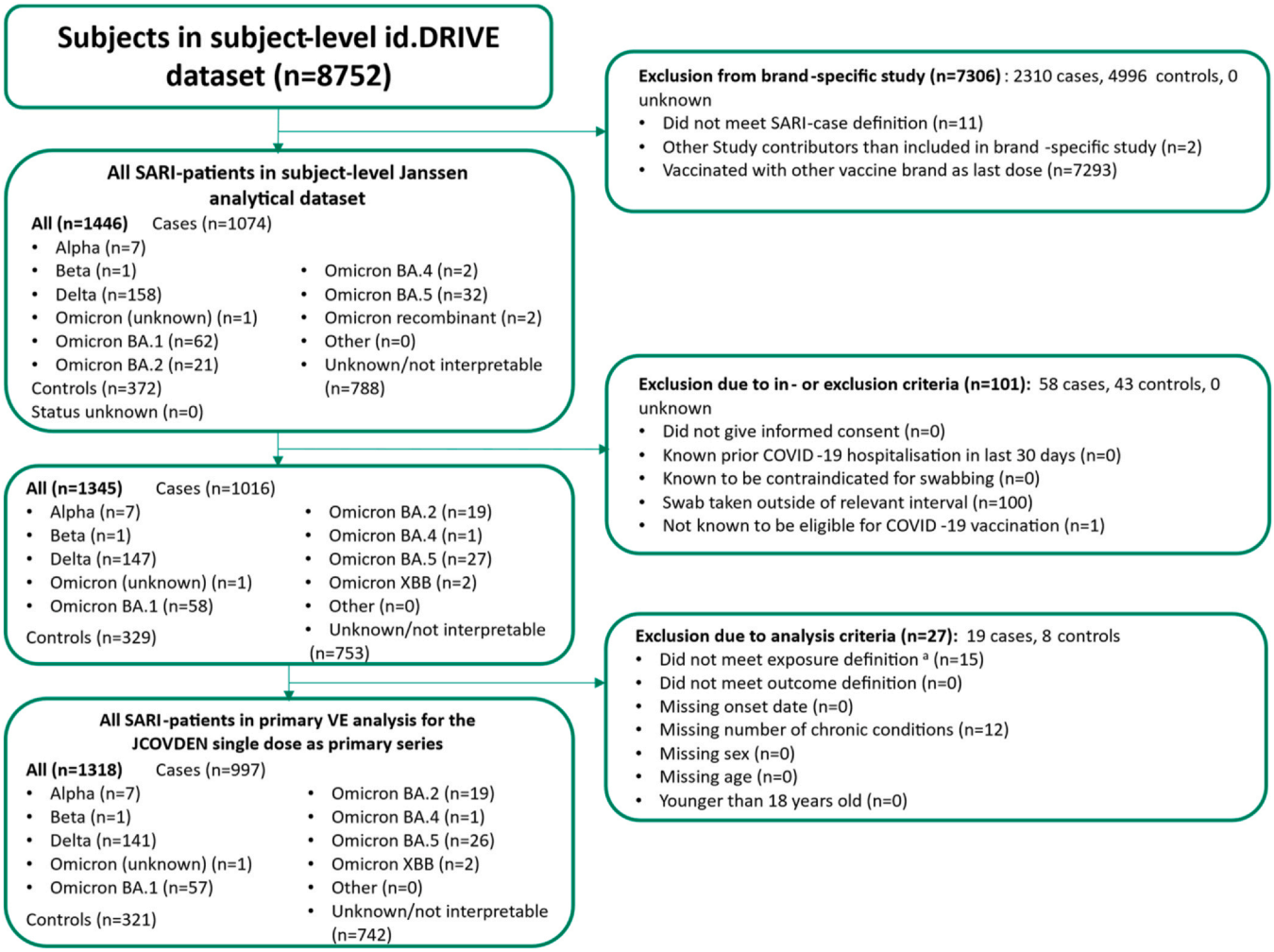

Fig. 1. Attrition diagram of primary COVID-19 vaccine effectiveness analysis for the JCOVDEN single-dose primary series. Abbreviations: n, number; SARI, severe acute respiratory infection; VE, vaccine effectiveness. [a] With a single-dose of JCOVDEN ≥ 14 days prior to SARI symptom-onset.

onset between June 2021 and February 2022 (76 %) and were retrospectively enrolled (57 %).

Overall, the median age was 57 years old (lower, upper quartile: 43; 71), 44 % (n = 584) of all SARI patients enrolled were female, 60 % (785) had at least one of the studied chronic conditions, and 5 % (72) were patients with immunodeficiency. Patient characteristics by case-control status are shown in Table 3. Medical history of prior SARS-CoV-2 infection was unknown for 24 % of the participants. Collected variables with ≥ 25 % missingness included body mass index, smoking history, viral respiratory co-infection, anti-pneumococcal and -influenza vaccination status, prophylactic and therapeutic medicines and information about health care workers.

In-hospital death occurred in 10 % (131) of the participants (12 % of all COVID-19 cases and 5 % of all test-negative controls). Compared to study participants alive at discharge, those who died in the hospital had a higher median age and higher number of chronic conditions (> 35 % have ≥3 chronic conditions). Among those alive at discharge, 186 were admitted to the ICU during their hospital stay (17 % of all COVID-19 cases and 4 % of all test-negative controls). Progression risks (proportion deceased and proportion of ICU admissions among hospitalised; proportion deceased among those admitted to ICU) were similar between unvaccinated and vaccinated COVID-19 cases (Table 4). The mean length of hospital stay among COVID-19 cases discharged alive was 2.6 days (95 % Confidence Interval [CI] −6.09; 0.82). Vaccinated individuals had shorter stays than the unvaccinated population (10.8 versus 13.4 days), whereas the median length of stay was similar between the groups (7–8 days).

COVID-19 vaccine effectiveness

The overall confounder-adjusted VE estimate of JCOVDEN single-dose against hospitalisation was 55.6 % (95 % CI 23.6; 74.2) using GEE as an estimating model, for a median time since vaccination of 146 days (interquartile range [IQR] 106; 210) (Table 5). Using GAM in place of GEE resulted in a slight increase of COVID-19 VE against hospitalisation to 59.0 % (95 % CI 27.5; 76.8). Similar results were obtained for the AUC of spline-based VE estimates up to 6 months (53.4 % [95 % CI 29.2; 77.6]).

COVID-19 VE against hospitalisation decreased with increasing age categories (Table 5). Using GEE, the VE reached 61.6 % (95 % CI 16.2; 82.4) in the 18–49 age group, 57.7 % (95 % CI 3.4; 81.5) in the 50–64 age group, and 40.8 % (95 % CI −6.0; 66.9) in the ≥ 65 group, albeit with wide CIs. Patients with no chronic conditions showed a higher COVID-19 VE (76.0 % [95 % CI 53.2; 87.7]) compared to patients with at least one studied chronic condition (45.8 % [95 % CI −3.7; 71.7]) but with a shorter median time since vaccination (Table 5). Similar trends in VE by age group and by number of chronic conditions were found when using GAM. Numbers were too low to produce precise VE estimates in subjects with immunodeficiency.

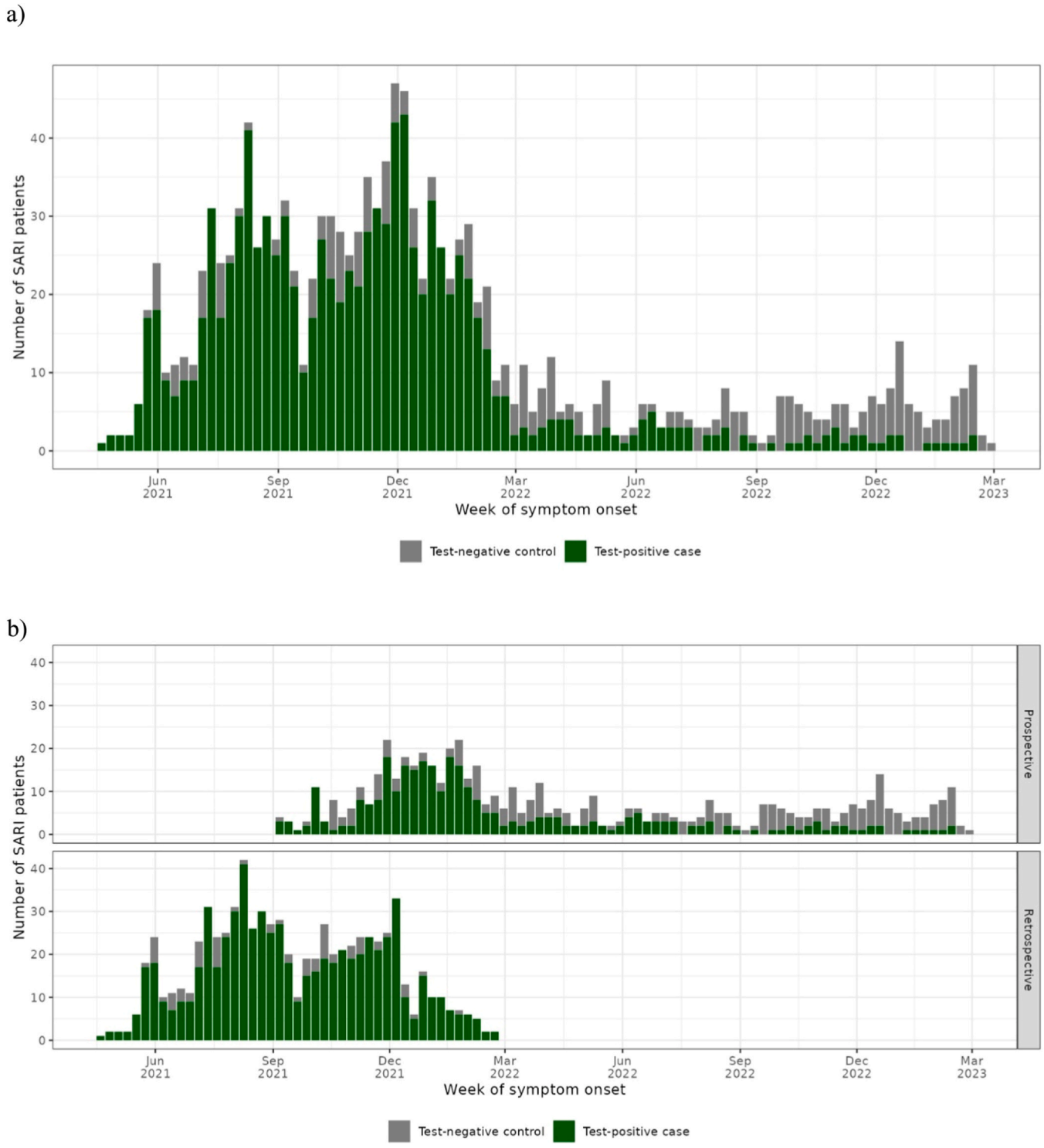

Fig. 2. Number of SARI patients enrolled in Janssen COVID-19 vaccine effectiveness study according to SARS-CoV-2 test status over time, a) overall and b) by type of enrolment (prospective and retrospective). Abbreviation: SARI, severe acute respiratory infection.

Table 6 presents JCOVDEN single-dose COVID-19 VE against hospitalisation according to time since vaccination. Most precise VE estimates were obtained for the interval > 12 and ≤ 25 weeks since vaccination, reaching 59.2 % (95 % CI 25.0; 77.8) using GEE and 63.4 % (95 % CI 18.6; 83.6) with GAM. The VE estimates for the other intervals had low precision, as indicated by the wide CIs.

Variant characterisation based on sequencing was only available for 27 % of the test-positive cases. Using the available results, VE estimates by variant were most precise when combined for all subvariants of Omicron, with 77.8 % (95 % CI 48.8; 90.4) using GEE and 82.5 % (95 % CI 20.5; 96.1) using GAM (Table 7). Due to an insufficient number of cases, VE was not estimable for the Alpha, Beta, and other Omicron subvariants. To complement VE estimates by variant, calendar time periods based on strain circulation and dominance, as reported by ECDC and GISAID were used as variant-proxy. The GEE-based VE was most precise for the Delta

Table 3
Characteristics of JCOVDEN vaccine effectiveness study participants according to SARS-CoV-2 test status.

Study participants	Total, n (%) 1318 (100)	Test-negative controls, n (%) 321 (100)	Test-positive cases, n (%) 997 (100)
Sex			
Male	734 (56)	192 (60)	542 (54)
Female	584 (44)	129 (40)	455 (46)
Age			
Years, median (lower, upper quartile)	57 (43, 71)	60 (46, 74)	55 (43, 69)
18–49 y	478 (36)	101 (31)	377 (38)
50–64 y	372 (28)	78 (21)	294 (29)
≥ 65 y	468 (36)	142 (44)	326 (33)
Country and Study Contributor			
Austria	390 (30)	4 (1)	386 (39)
Klinik Favoriten	*390 (30)*	*4 (1)*	*386 (39)*
Belgium	266 (20)	44 (14)	222 (22)
CHU St Pierre	*49 (4)*	*33 (10)*	*16 (2)*
UZA	*122 (9)*	*8 (2)*	*114 (11)*
GHdC	*95 (7)*	*3 (1)*	*92 (9)*
Italy	141 (11)	48 (15)	93 (9)
CIRI-IT	*141 (11)*	*48 (15)*	*93 (9)*
Spain	521 (40)	225 (70)	296 (30)
VAHNSI	*176 (13)*	*86 (27)*	*90 (9)*
GTPUH	*213 (16)*	*91 (28)*	*122 (12)*
HUVH	*132 (10)*	*48 (15)*	*84 (8)*
Chronic condition[a]			
Asthma	87 (7)	38 (12)	49 (5)
Lung disease	199 (15)	85 (26)	114 (11)
Cardiovascular disease	289 (22)	93 (29)	196 (20)
Hypertension	477 (36)	112 (35)	365 (37)
Chronic kidney disease	130 (10)	36 (11)	94 (9)
Chronic liver disease	54 (4)	18 (6)	36 (4)
Type 2 diabetes	258 (20)	49 (15)	209 (21)
Cancer	102 (8)	40 (12)	62 (6)
Immunodeficiency (or organ transplant)[b]	72 (5)	28 (9)	44 (4)
Number of chronic conditions			
0	533 (40)	88 (27)	445 (45)
≥ 1	785 (60)	233 (73)	552 (55)
Body mass index (BMI), kg/m^2			
Underweight (BMI < 18.5)	25 (2)	8 (2)	17 (2)
Normal/healthy weight (BMI ≥18.5 to < 25.0)	238 (18)	89 (28)	149 (15)
Overweight (BMI ≥25.0 to < 30.0)	280 (21)	53 (17)	227 (23)
Obese (BMI ≥30.0)	294 (22)	44 (14)	250 (25)
No information/Missing[c,d]	481 (36)	127 (40)	354 (36)
Level of severity			
Hospital admission without ICU admission and without in-hospital death	1001 (76)	292 (91)	709 (71)
ICU admission without in-hospital death	186 (14)	14 (4)	172 (17)
In-hospital death	131 (10)	15 (5)	116 (12)
Length of stay			
< 10 days	771 (58)	238 (74)	533 (53)
10–29 days	446 (34)	72 (22)	374 (38)
≥ 30 days	101 (8)	11 (3)	90 (9)
Viral respiratory coinfection			
No	948 (72)	191 (60)	757 (76)
Yes	43 (3)	0 (0)	43 (4)
No information/Missing[c,d]	327 (25)	130 (40)	197 (20)
Pregnancy			
No	495 (85)	123 (95)	372 (82)
Yes	36 (6)	2 (2)	34 (7)
No information/Missing[c,d]	51 (8)	6 (3)	47 (10)
Prior COVID-19 infection			
No	965 (73)	159 (50)	806 (81)
Yes – clinical diagnosis	4 (0)	2 (1)	2 (0)
Yes – laboratory-confirmed	30 (2)	20 (6)	10 (1)
No information/Missing[c,d]	319 (24)	140 (44)	179 (18)
Vaccinated against influenza within 12 months prior to SARI hospital admission			
No	720 (55)	269 (84)	451 (45)
Yes	59 (4)	30 (9)	29 (3)
No information/Missing[c,d]	539 (41)	22 (7)	517 (52)
Received any pneumococcal vaccine			
No	667 (51)	260 (81)	407 (41)
Yes	70 (5)	38 (12)	32 (3)
No information/Missing[c,d]	581 (44)	23 (7)	558 (56)
Smoking history			
Never-smoker	483 (37)	119 (37)	364 (37)
Ex-smoker	220 (17)	74 (23)	146 (15)
Occasional smoker	23 (2)	13 (4)	10 (1)
Daily smoker	156 (12)	76 (24)	80 (8)
No information/Missing[c,d]	436 (33)	39 (12)	397 (40)

(*continued on next page*)

Table 3 (*continued*)

Study participants	Total, n (%) 1318 (100)	Test-negative controls, n (%) 321 (100)	Test-positive cases, n (%) 997 (100)
Long-term care facility residence[e]			
No	1258 (95)	312 (97)	946 (95)
Yes	14 (1)	4 (1)	10 (1)
No information/Missing[c,d]	46 (4)	5 (2)	41 (5)
Healthcare worker			
No	978 (74)	228 (71)	750 (75)
Yes	3 (0)	0 (0)	3 (0)
No information/Missing[c,d]	337 (26)	93 (29)	244 (24)
Anti-SARS-CoV-2 drugs indicated for pre- and/or post-exposure prophylaxis			
No	548 (42)	48 (15)	500 (50)
Yes	0 (0)	NA	NA
No information/Missing[c,d]	770 (58)	273 (85)	497 (50)
Anti-SARS-CoV-2 drugs indicated for treatment post-symptom onset			
No	340 (26)	52 (16)	288 (29)
Yes	234 (18)	0 (0)	234 (23)
No information/Missing[c,d]	744 (56)	269 (84)	475 (48)

Abbreviations: %, percentage; CHU, Centre Hospitalier Universitaire; CIRI-IT, Centro Interuniversitario per la Ricerca sull'Influenza e le altre Infezioni Trasmissibili; GHdC, Grand Hôpital de Charleroi; GTPUH, Hospital Universitari Germans Trias i Pujol; HUVH, Hospital Universitari Vall d'Hebron; ICU, intensive care unit; n, number; NA, not applicable; UZA, Universitair Ziekenhuis Antwerpen; VAHNSI, Valencia Hospital Network for the Study of Infectious Diseases.

[a] Patients may be included in multiple categories, so percentages do not sum to 100

[b] For VAHNSI, HIV-infected patients, transplant recipients and patients with iatrogenic-immunodeficiency were not included in the immunodeficiency group

[c] Reported as "no information" in the electronic case report form (eCRF)

[d] eCRF was not completed for this non-mandatory variable (empty cell)

[e] For VAHNSI, Long-term care facility residents were excluded during SARI screening

predominant calendar time period (1 Aug 2021 – 30 Nov 2021), reaching 51.2 % (21.7; 69.6). The precision of other calendar time periods and using GAM was low.

In the first sensitivity analysis, restricting the maximum time between symptom-onset and swab to ≤ 3 days resulted in the exclusion of 777 SARI patients, which increased median time since vaccination from 146 days to 155 days (IQR 106; 227) and increased GEE-based VE from 55.6 % (95 % CI 23.6; 74.2) to 70.5 % (95 % CI 34.4; 86.8). For the second sensitivity analysis, extending the maximum time between hospital admission and swab from 24 to 72 hours added 99 SARI patients to the analysis. The GEE-based VE was 57.2 % (95 % CI 32.9; 72.7) for a median time since vaccination of 151 days (IQR 108; 216).

The third sensitivity analysis applied the WHO SARI case definition instead of the modified ECDC SARI case definition. Of the 709 SARI excluded for this analysis, 43 (6.1 %) had symptom-onset of > 10 days, and the rest were excluded based on clinical criteria. Using the WHO SARI case definition lowered the median time since vaccination to 136 days (IQR 103; 195) and increased GEE-based VE to 64.8 % (95 % CI 11.4; 86.0).

Finally, when only including the prospectively enrolled patients, the median time since vaccination was 188 days (IQR 136; 328) and GEE-based VE were 49.8 % (95 % CI 12.0; 71.2).

Challenges and lessons learnt

Table 8 summarises the multiple challenges faced during the conduct of this study, the impact that they had, and the mitigation strategies applied. These challenges were related to the dynamics of the pandemic and resulting public health measures, vaccine introduction and uptake, and differences in local procedures across the multiple participating sites.

Discussion

This multi-centre TNCC study demonstrates VE of the JCOVDEN single-dose primary series against COVID-19 hospitalisation in persons 18 years and older. We estimated VE at 55.6 % (95 % CI 23.6; 74.2) for a median time since dose of approximately five months (146 days). Results were obtained from a pooled dataset using data collected over 22 months by eight Study Contributors across four European countries.

A large network allowed the successful execution of a VE study despite a lower uptake of JCOVDEN compared to other COVID-19 vaccines in Europe. Vaccination with JCOVDEN in Europe started in April 2021, several months into the primary vaccination campaigns and less than 6 months before the start of the booster vaccination campaigns. This resulted in a limited number of persons eligible for enrolment in a study on JCOVDEN single-dose exposure. Further complexity arose from identifying TTS as an adverse event of the vaccine, which led to various public health responses mid-campaign, from interruptions of roll-out to modifications in the recommended age for use. In several countries, including Belgium, Italy and Spain, JCOVDEN use has become limited to older age groups, with thresholds varying from 40 to 60 years old.

Overall, JCOVDEN VE point estimates have generally been higher than those we report here (~70–85 %) [16–22], all but for a

Table 4
Progression risk among test-positive cases (proportion deceased and proportion of ICU admissions among hospitalised; proportion deceased among those admitted to ICU).

Test-positive cases	Hospitalised N	In-hospital death[a], no ICU N	In-hospital death[a], no ICU % (95 % CI)[b]	ICU (all) N	ICU % (95 % CI)[b]	ICU and in-hospital death[a] N	ICU and in-hospital death[a] % (95 % CI)[c]
Vaccinated[d]	59	3	5.1 (1.1; 14.1)	11	18.6 (9.7; 26.9)	3	27.3 (6.0; 61.0)
Unvaccinated	938	49	5.2 (3.9; 6.8)	225	24.0 (21.3; 26.9)	61	27.1 (21.4; 33.4)

Abbreviations: %, percentage; CI, confidence interval; ICU, intensive care unit; N, number.

[a] In-hospital death, during or after ICU discharge

[b] Among hospitalised patients

[c] Among ICU patients

[d] With a single-dose of JCOVDEN ≥ 14 days prior to SARI symptom-onset.

Table 5
Overall JCOVDEN vaccine effectiveness and according to age group and number of chronic conditions.

Participant's characteristics	Test-negative controls N (%)	Test-positive cases N (%)	Time since JCOVDEN single-dose in days Median (IQR)	Confounder-adjusted[a] VE % (95 % CI), using GEE	Confounder-adjusted[a] VE % (95 % CI), using GAM
Vaccination status					
Vaccinated[b]	49 (45)	59 (55)	146 (106; 210)	55.6 (23.6; 74.2)	59.0 % (27.5; 76.8)
Unvaccinated	272 (22)	938 (78)			
Age group of interest (years)					
18–49					
Vaccinated[b]	20 (53)	18 (47)	151 (90; 252)	61.6 (16.2; 82.4)	70.9 % (22.4; 89.1)
Unvaccinated	81 (18)	359 (82)			
50–64					
Vaccinated[b]	16 (42)	22 (58)	156 (119; 189)	57.7 (3.4; 81.5)	47.1 % (−39.4; 79.9)
Unvaccinated	62 (19)	272 (81)			
≥ 65					
Vaccinated[b]	13 (41)	19 (59)	134 (108; 200)	40.8 (−6.0; 66.9)	41.0 % (−77.3, 80.4)
Unvaccinated	129 (30)	307 (70)			
Number of chronic conditions					
No chronic condition					
Vaccinated[b]	12 (34)	23 (66)	119 (50; 172)	76 (53.2; 87.7)	80.6 % (47.2; 92.9)
Unvaccinated	76 (15)	422 (85)			
≥ 1 chronic conditions					
Vaccinated[b]	37 (51)	34 (49)	163 (116; 237)	45.8 (−3.7; 71.7)	47.8 % (−5.3; 74.1)
Unvaccinated	196 (28)	516 (72)			

Abbreviations: %, percentage; CI, confidence interval; GAM, Generalised additive model (secondary analysis); GEE, generalised estimating equations (primary analysis); IQR, interquartile range; N, number; VE, vaccine effectiveness.
[a] Adjusted for onset date, number of chronic conditions, sex, and age
[b] With a single-dose of JCOVDEN ≥ 14 days prior to SARI symptom-onset.

Table 6
JCOVDEN vaccine effectiveness by non-cumulative time since vaccination.

Time since JCOVDEN single-dose	Vaccination status	Test-negative controls N (%)	Test-positive cases N (%)	Confounder-adjusted[a] VE% (95 % CI), using GEE	Confounder-adjusted[a] VE % (95 % CI), using GAM
≥ 14 days and ≤ 12 weeks	Vaccinated[b]	5 (28)	13 (72)	52.4 (2.8; 76.7)	68.5 % (−26.5; 92.2)
	Unvaccinated	272 (22)	938 (78)		
> 12 and ≤ 25 weeks	Vaccinated[b]	20 (40)	30 (60)	59.2 (25.0; 77.8)	63.4 % (18.6; 83.6)
	Unvaccinated	272 (22)	938 (78)		
> 25 and ≤ 52 weeks	Vaccinated[b]	10 (40)	15 (60)	35 (−50.2; 71.9)	31.8 % (−93.8; 76.0)
	Unvaccinated	272 (22)	938 (78)		
> 52 weeks	Vaccinated[b]	14 (93)	1 (7)	79.3 (−79.0; 97.6)	79.5 % (−80.8; 97.7)
	Unvaccinated	272 (22)	938 (78)		

Abbreviations: %, percentage, CI, confidence interval; GAM, Generalised additive model (secondary analysis); GEE, generalised estimating equations (primary analysis); N, number; VE, vaccine effectiveness.
[a] Adjusted for onset date, number of chronic conditions, sex, and age
[b] With a single-dose of JCOVDEN ≥ 14 days prior to SARI symptom-onset

Hungarian study that found 47.2 % (95 % CI 41.2; 52.6) in 16- to 64-year-olds [23]. These studies, however, differ in setting, study period, dominant variant, study population, and methods, including testing strategy. Even when studies use a SARI case-definition, the definitions can differ, affecting the populations being studied and the results being produced. In this study, we showed that using the stricter WHO SARI case definition rather than the modified ECDC SARI case definition would modify results by increasing VE by nine percentage points (64.8 % [95 % CI 11.4; 86.0]). In another sensitivity analysis, we found that restricting the time between symptom-onset and swab date to 3 days increased VE by 15 percentage points (70.5 % [95 % CI 34.4; 86.8]). This could indicate the occurrence of misclassification bias due to a drop in SARS-CoV-2 RT-PCR sensitivity with increasing time since symptom-onset and illustrates how testing strategies may affect VE estimates [24,25]. Overall, our results support the need for harmonised methodology across VE studies to allow for correct comparison, as done by the id.DRIVE Consortium across its post-authorisation studies [7].

The variables included in the statistical model and how they are treated also influence VE results and their interpretation [26]. In this study, we performed a secondary analysis using GAM instead of GEE. Using GAM resulted in a minor increase of VE against hospitalisation by four percentage points (59.0 % [95 % CI 27.5; 76.8]) and greater uncertainty around the estimates when stratifying results. Results from GEE and GAM give complementary information, as GEE VE estimates compare vaccinated and unvaccinated subjects across clusters (Study Contributors). In contrast, GAM VE estimates compare vaccinated and unvaccinated subjects within the same cluster.

The VE against hospitalisation was affected by multiple features, including age, presence of chronic conditions, time since vaccination and SARS-CoV-2 genetic variant. By age group, VE showed lower point estimates at older ages, with the lowest point estimates for those ≥ 65 years old (40.8 % [95 % CI −6.0; 66.9]), as previously shown [18–22,27]. Similarly, the presence of at least one of the studied chronic conditions was associated with a lower VE point estimate (45.8 [95 % CI −3.7; 71.7]). Lower VE in these risk groups could be explained by a blunting of vaccine responses due to immunosenescence and/or immunosuppressing conditions [28]. However, our results are to be interpreted with caution as these VE point estimates had wide and overlapping CIs, indicating low to medium levels of certainty.

When performing estimates by time since vaccination, JCOVDEN VE against COVID-19 hospitalisation remained stable for at least 6 months after immunisation. These results concur with previous immunogenicity and VE studies that have reported a slow waning of protection against COVID-19 infections and hospitalisations after the

Table 7
JCOVDEN vaccine effectiveness by variant and by calendar time according to variant dominance.

Variant exposure	Vaccination status	Test-negative controls N (%)	Test-positive cases N (%)	Time since JCOVDEN single-dose Median (IQR)	Confounder-adjusted[a] VE % (95 % CI), using GEE	Confounder-adjusted[a] VE % (95 % CI), using GAM
Genetic variant						
Delta	Vaccinated[b]	49 (74)	17 (26)	160 (106; 279)	40.5 (−47.0; 75.9)	33.0 % (−67.1; 73.1)
	Unvaccinated	272 (69)	124 (31)			
Omicron (all subvariants)	Vaccinated[b]	49 (94)	3 (6)	184 (116; 384)	77.8 (48.8; 90.4)	82.5 % (20.5; 96.1)
	Unvaccinated	272 (73)	101 (27)			
Omicron BA.1 subvariant	Vaccinated[b]	49 (94)	3 (6)	184 (116; 384)	64.5 (34.5; 80.8)	82.7 % (−70.9; 98.2)
	Unvaccinated	272 (83)	54 (17)			
Calendar time (dominant strain(s))						
1 May 2021 – 31 Jul 2021 (Gamma, Beta, Alpha and Delta)	Vaccinated[b]	1 (50)	1 (50)	40 (33; 46)	68.8 (−7.5; 90.9)	−21.7 % (−9496.6; 98.5)
	Unvaccinated	29 (15)	162 (85)			
1 Aug 2021 – 30 Nov 2021 (Delta predominant)	Vaccinated[b]	22 (39)	35 (61)	112 (74; 135)	51.2 (21.7; 69.6)	62.1 % (0.2; 85.6)
	Unvaccinated	39 (9)	414 (91)			
1 Dec 2021 – 31 Dec 2021 (Delta, Omicron BA.1)	Vaccinated[b]	4 (20)	16 (80)	170 (144; 186)	40.4 (−74.1; 79.6)	16.2 % (−296.2; 82.3)
	Unvaccinated	12 (9)	129 (91)			
1 Jan 2022 – 30 Apr 2022 (Omicron BA.1 and BA.2)	Vaccinated[b]	5 (50)	5 (50)	206 (190; 260)	52.7 (−37.5; 83.7)	54.6 % (−153.0; 91.8)
	Unvaccinated	56 (25)	165 (75)			
1 May 2022 – 30 Jun 2022 (Omicron BA.2, BA.4 and BA.5)	Vaccinated[b]	2 (100)	0 (0)	275 (271; 279)	NE	NE
	Unvaccinated	15 (41)	22 (59)			
1 Jul 2022 – 30 Sep 2022 (Omicron BA.5 predominant)	Vaccinated[b]	7 (88)	1 (12)	392 (359; 433)	76.1 (11.9; 93.5)	NE
	Unvaccinated	30 (60)	20 (40)			
1 Oct 2022 – 28 Febr 2023 (Omicron BA.5, BQ.1, BA.2.7, and XBB)	Vaccinated[b]	8 (89)	1 (11)	485 (464; 533)	−32.9 (−1137.5; 85.7)	−12.3 % (−1189.3; 90.2)
	Unvaccinated	91 (78)	26 (22)			

Abbreviations: %, percentage; CI, confidence interval; IQR, interquartile range; GAM, Generalised additive model (secondary analysis); GEE, generalised estimating equations (primary analysis); N, number; NE, not estimable; VE, vaccine effectiveness.
[a] Adjusted for onset date, number of chronic conditions, sex, and age
[b] With a single-dose of JCOVDEN ≥ 14 days prior to SARI symptom-onset

JCOVDEN primary series [29]. The sample size neither allowed further stratification of time since vaccination intervals by risk group nor could conclude on the dynamics of protection waning beyond six months.

Delta was the dominant SARS-CoV-2 variant during the first eight months of the study, while the Omicron BA.1 variant emerged in December 2021 and rapidly became predominant across the participating countries for approximately four months. The remainder of the study period was marked by the sequential emergence and co-circulation of several Omicron subvariants, namely BA.1, BA.2, BA.4; BA.5, BQ.1, BA.2.75, and XBB. By variant, VE estimates showed persisting protection against Omicron and its subvariant BA.1, further supporting lasting protection by JCOVDEN [19,21]. However, the proportion of sequenced samples was low (27 %), and VE was non-estimable for the less prevalent variants. This low sequencing rate was due to the high proportion of retrospectively enrolled patients, laboratory-related issues (e.g., inadequate sampling or insufficient viral load), and logistic problems. Conversely, when using calendar time periods as a proxy for circulating variant, the most precise VE estimates were obtained for the Delta predominant period (51.2 % [95 % CI 21.7; 69.6]).

In general, disentangling the complex interactions of time-varying features, including vaccine recommendations, circulating variants, or waning of immunity, has proven challenging across COVID-19 VE studies [30]. When interpreting our VE estimates, the role of selection bias needs to be carefully considered. Indeed, populations at highest risk of exposure (e.g., HCW) and of severe COVID-19 (older age, subjects with chronic conditions and/or immunodeficiency) were targeted and prioritised for both primary and booster vaccinations, and 32 % of adults 60 years and above had already received a first COVID-19 vaccine dose prior to JCOVDEN market availability [4]. In addition, the study population was limited to subjects either unvaccinated or vaccinated with a single-dose of JCOVDEN, excluding those who went on to receive a booster dose. These factors may have led to a selective population that is insufficiently representative of the population eligible for COVID-19 vaccination, particularly for the later periods of the study (e.g., booster campaign period, Omicron BA.1 dominating period).

One of the objectives of the present paper was to highlight the lessons learnt while designing, setting-up, and conducting this study to support future (pandemic) VE studies. Strengths, complexities, challenges, and mitigation measures are summarised and provided in a structured manner in a table format (Table 8). Due to the low vaccine uptake of JCOVDEN and the ineligibility of numerous patients, high recruitment was required to meet the study objectives. To increase the sample size, additional Study Contributors, countries and retrospective data were included as the study progressed. However, multiple site and country differences (regarding vaccine recommendations, vaccine roll-out, SARS-CoV-2 incidence, data collection periods and recruitment) led to significant inter-Study Contributor variation and clustering of outcomes within sites. Clustering occurred due to local specificities (e.g., Klinik Favoriten was a referent COVID-19 hospital, leading to near exclusive recruitment of COVID-19 cases) or epidemiological realities (e.g., a cluster of unvaccinated cases during a local COVID-19 surge early in the vaccine campaign). As clustering negatively impacts the precision of results for a given sample size [31], the additional enrolment did not achieve the desired outcome to increase precision around VE estimates.

The other main limitation of the study was the insufficient or absence of data to adjust for confounders such as prior infection, chronic conditions other than those captured (e.g., BMI or neurological disease), healthcare-seeking behaviour (e.g., vaccination against influenza or pneumococcal disease), or ethnicity and socio-economic status [32].

Despite these limitations, our study has several strengths. It is the first published multi-country European study producing brand-specific results for JCOVDEN. By mutualising efforts across different European countries, the study achieved higher enrolment than regional or country-based SARI sentinel studies could obtain. Additionally, the 22-month-long study period allowed us to

Table 8
id.DRIVE JCOVDEN COVID-19 vaccine effectiveness study challenges and mitigation pathways.

Factor	Pathway	Impact on JCOVDEN Study	Mitigation Strategy and Lessons Leant
Pandemic	Test-negative controls limited during COVID−19 surge periods due to precautionary behaviours, reduction of other circulating viruses	Temporal differences in case and control hospitalisations and different case:control ratios by site related to timing of enrolment	Adjustment for onset date in models
	Fluctuation in non-COVID respiratory virus activity related to changes in mandates and adherence to non-pharmaceutical interventions		Calendar time stratified analysis
	Changes in transmissibility and severity with SARS-CoV−2 variant evolution	Time-specific data required for each variant Retrospective participant enrolment limited sequencing and sample size for variant-specific analysis VE against lesser prevalent variants could not be estimated	Variant-specific analyses Multiple imputation or data augmentation techniques should be considered for future id.DRIVE studies with low sequencing rates
	Prior COVID infection	Prior infection status could influence VE estimates. There were insufficient data (quality and quantity) to stratify or adjust for prior infection in analysis	Identified as a limitation of the study
	COVID−19 (SARI) case-definition	Different SARI and COVID−19 case definitions used in equivalent VE studies (e.g., ECDC verse WHO case-definition)	Broader case definition used for inclusion and sensitivity analysis preformed using the more stringent definition Importance of harmonised and standardisation across VE protocols
COVID−19 vaccination	Country-specific recommendations by age and risk groups	Time-varying features that may influence VE results	VE estimates were adjusted for symptom-onset data in all analyses Identified as a limitation of the study
		As the eligibility criteria limited analysis to unvaccinated or vaccinated with a single dose of JCOVDEN, the study population may not be a representative sample of the population recommended for vaccination	Identified as a limitation of the study
	Late recommendation and low uptake of JCOVDEN in the EU	Lower uptake of JCOVDEN than predicted meant higher sample sizes requirements than initially considered	Expansion of the network to include additional study sites
		Lack of increase in precision around VE estimates despite the increase in sample size (expansion to additional study sites)	Post-hoc analysis showed clustering of outcomes. Clustering can lead to a high intraclass correlation coefficient (ICC; correlation between two randomly selected members of the same cluster being a test-positive case). This in turn negatively impacts the precision of results for a given sample size.
Study Sites	Differences in clinical definition of immunodeficiency	Clinical definition of immunodeficiency was different at one site, which could affect VE results for this population	Corrected for future id.DRIVE VE studies. VE in immunodeficient subjects not reported (data quality and small sample size)
	Certain sites became COVID−19 specialised-units, limiting further the possibility of recruiting controls	Site differences in case and control ratios. Contribution to high ICC	Now part of feasibility assessments of sites Avoid activation of such sites when possible
	Limited vaccine data for deceased at Belgian sites: individual vaccine records could no longer be retrieved from the national vaccine registry once a person is deceased. Thus, when collecting retrospective data, only hospital medical records could be used to obtain exposure data of persons that were dead by the time of the data collection.	Limited vaccine data for deceased patients may have led to potential selection bias in data collected retrospectively with a higher rate of exclusion in the subgroup of deceased patients due to incomplete vaccination data. However, this potential bias is considered negligible as it would only concern a limited number of subjects (id.DRIVE dataset).	Documentation of all site and country-specific differences are required in such studies to allow for correct interpretation of the data and evaluation of potential bias
	Challenges for identifying SARI during retrospective enrolment at specific sites: while positive COVID−19 PCR results from laboratory records helped identify cases, the screening of all admitted patients (regardless of diagnosis) made it impossible to use negative test results for SARI identification	Unfavourable case-control ratios	Avoidance of retrospective data collection, when possible

Abbreviations: COVID-19,coronavirus disease 2019; ECDC, European Centre for Disease Prevention and Control; EU, European Union; ICC, interclass correlation coefficient; SARI, severe acute respiratory infection; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TTS, thrombocytopenia syndrome; VE, vaccine effectiveness; WHO, World Health Organization.

investigate potential waning over time and protection against several variants. Furthermore, the study is conducted within the master id.DRIVE COVID-19 VE study, which applies a common protocol and eCRF. This ensures standardisation across its EMA-destined post-marketing studies and across countries despite heterogeneous vaccine recommendations and roll-out.

Conclusions

The JCOVDEN single-dose primary series protected against COVID-19 hospitalisation with enduring levels for at least 6 months. Although JCOVDEN use has drastically dropped, these results are essential for post-authorisation VE monitoring, contribute to the

increasing pool of knowledge on viral-vector vaccines, and confirm the capability of the id.DRIVE platform. Lower VE estimates in older age groups and those with chronic conditions are to be considered and further monitored for equivalent vaccines. Finally, the challenges and lessons learnt from this study are important considerations for future VE studies, particularly for those set in pandemic settings and/or situations of low vaccine uptake.

Contributors

This study was designed by members of the COVIDRIVE consortium, now id.DRIVE, in collaboration with the Ad26.COV2.S (JCOVDEN) Marketing Authorisation Holder, Janssen. LD was involved in the coordination of the COVIDRIVE study. AM-I, AOS, AA, CM, GI, IC, GLtK, SB, SO-R, and XH are principal investigators at the Study Contributors (study sites) and were responsible for data collection and coordination at their respective sites. P95 and Janssen collaborated with investigators at study sites in data collection. The data were analysed by AD and KYN, and interpreted by CW-T, ECN, LdM, NV, KB and NP. This manuscript was written by CW-T, ECN, NV, and NP. AM-I, AD, AOS, AA, CM, GI, IC, KYN, LD, LdM, GLtK, SB, SO-R, XH, and KB critically reviewed the manuscript. All authors approved of the final version of this manuscript, and all authors are accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data sharing statement

De-identified data that underlie the results reported in this article (text, tables, figures, and appendices) may be obtained in accordance to id.DRIVE data access policy.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **NP** declares employment by Janssen Pharmaceuticals and ownership of Janssen Pharmaceuticals shares. **ECN** declares employment by Janssen Pharmaceuticals and ownership of Janssen Pharmaceuticals stocks during the time of the study and the writing of the manuscript, and support for attending meetings and/or travel by Janssen Pharmaceuticals. **CW-T**, **KYN**, **LD**, **LdM**, **NV**, and **KB** are employed by P95. **AD** was employed by P95 during the time of the study and the writing of the manuscript. P95 received consulting fees from different COVID-19 vaccine manufacturers, including Janssen, for the id.DRIVE study. **KB** declares consulting fees from AstraZeneca, Bavarian Nordic, CureVac, Janssen, GSK, Pfizer, Novavax, Valneva and WHO, ownership of P95 stocks, and royalties for the book "Vaccination Programmes: epidemiology, monitoring, evaluation' by Hahné, Bollaerts, Farrington. **AOS** declares partial funding from Janssen, GlaxoSmithKline, Pfizer, and AstraZeneca of the hospital network for the identification of cases in The Valencia Region of Spain. **AM-I** declares as Co-PI from VAHNSI (FISABIO) that her foundation received funding from P95 via id.DRIVE to conduct the study. **SB** declares payment for lecture from GlaxoSmithKline and meeting invitation by MSD. **IC** declares support from Pfizer to attend a congress. **GLtK**, **AA**, **CM**, and **XH** declare no conflicts of interest. **SO-R** declares payment for presentations from GlaxoSmithKline and Sanofi. **GI** declares payment for participation as an expert in the Medical Education Steering Committee (MESC) Vaccines of 2021.

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