[A-338] Evaluating the Diagnostic Accuracy of Adverse Events of Special Interest Following Janssen COVID-19 Vaccine (JCOVDEN) Using the VAC4EU Validation Pipeline [1332]

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BACKGROUND

- The Ad26.COV2.S vaccine (marketed as JCOVDEN) was authorized in the EU in March 2021 for COVID-19 prevention and withdrawn in August 2024 after over 19 million doses were administered.
- The vaccine's risk management plan identified thrombosis with thrombocytopenia syndrome (TTS), Guillain-Barré syndrome (GBS), immune thrombocytopenia, and venous thromboembolism as important risks; myocarditis and pericarditis were considered as potential risks.
- Regulatory guidance (EMA, FDA) emphasizes the need for validation of adverse events of special interest (AESIs) in real-world data (RWD) studies.
- AESIs are often identified using diagnostic medical codes (e.g., ICD-10), which may not capture the full clinical context required for case validation.
- Case definitions for AESIs were based on those published by the Brighton Collaboration (BC), when available, and by VAC4EU clinical and epidemiological experts through literature review when not available.

OBJECTIVES

To estimate the positive predictive value (PPV) of diagnostic code-based medical algorithms for 11 prespecified AESIs across neurological, hematological/thrombotic, and cardiovascular disorders in a retrospective post-authorisation safety study (PASS) of JCOVDEN in Europe.

METHODS

Data sources:

- SIDIAP (Catalonia, Spain): 5.7 million active population
- VID (Valencia, Spain): 5 million active population

Inclusion criteria: At least one day of follow-up after vaccination and at least 12 months of enrolment in the data source at the start of follow-up.

Outcomes:

- The study assessed 11 AESIs identified following JCOVDEN vaccination.
- Cases were classified according to the Brighton Collaboration case definition level of certainty (LOC):

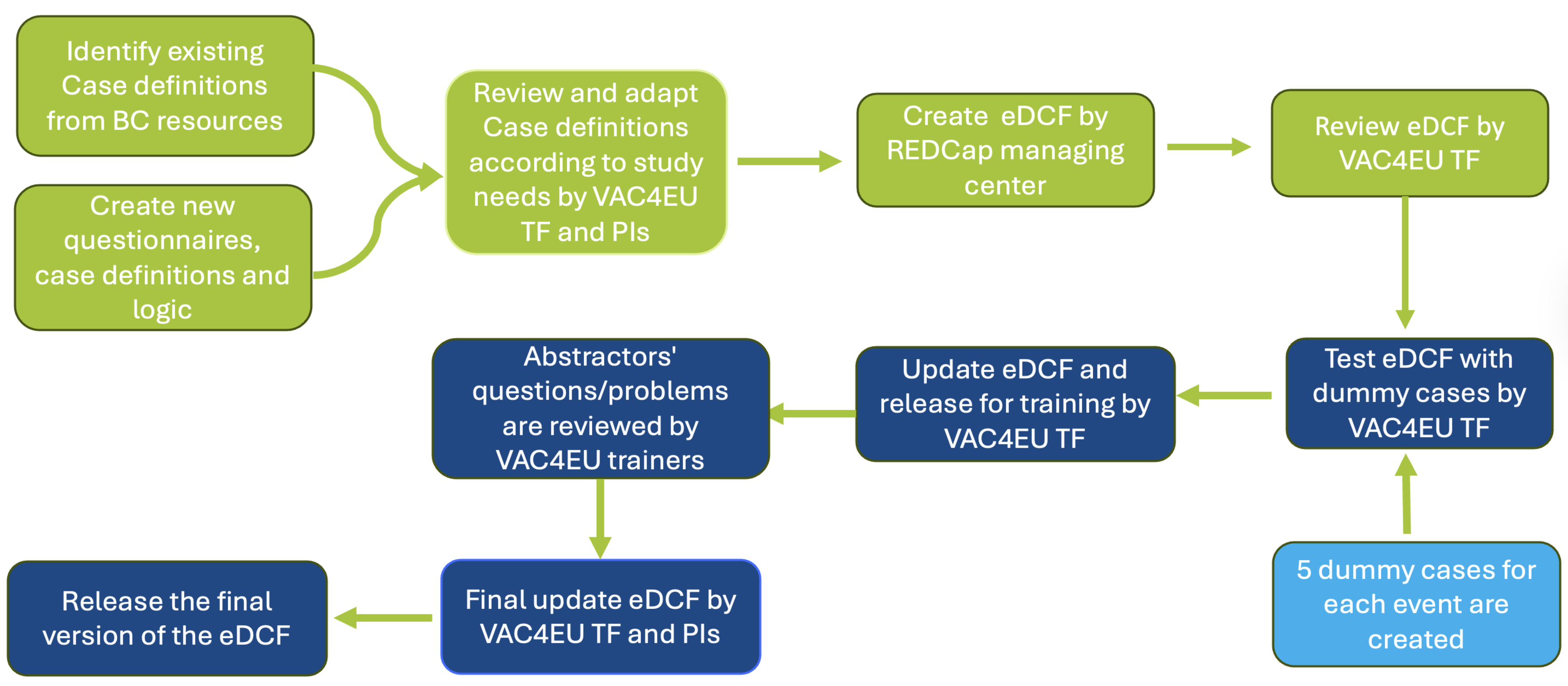
LOC1: Highest certainty, all major diagnostic criteria met with clear supporting evidence.
LOC 2: Most, but not all, criteria fulfilled, diagnosis still well supported.
LOC 3: Moderate certainty, key clinical features present but insufficient documentation for a higher level.
LOC 4a: Insufficient information to meet levels 1, 2, 3, or 5, but a confirmation of the diagnosis was provided by a specialist.
LOC 4b: Insufficient information available to meet levels 1, 2, 3, or 5. This level reflects a complete lack of relevant information for making a determination.
LOC 5: Available evidence contradicted the diagnosis, case did not meet the definition.

- **Strict PPV:** LOC1–3 / all validated cases (excluding LOC4b from the denominator)
- **Broad PPV:** LOC1–4a / all validated cases (excluding LOC4b from the denominator)
- All data processing followed GDPR-compliant decentralized analysis within the VAC4EU network using the ConcePTION Common Data Model.

Study design: A retrospective observational study using electronic healthcare data from two data sources. All levels of healthcare were used for case validation in VID, and hospital records were available for validation in SIDIAP.

Study Population: Individuals who received at least one dose of the COVID-19 vaccine (JCOVDEN) starting in April 2021 were followed from their first dose until one year later, or until they received another vaccine, a booster, experienced a specific AESI, or died.

Figure 1: The VAC4EU case validation pipeline



BC= Brighton Collaboration; TF=Task force; PI=Principal Investigator; eDCF=electronic data collection forms, REDCap=Research Electronic Data Capture.

RESULTS

A total of **323 AESI** cases were validated in JCOVDEN recipients across SIDIAP (only for CVST and TTS) and VID.
Positive predictive values (PPVs) varied substantially across AESIs, reflecting both diagnostic complexity and data source granularity.

High PPVs (>80%) were observed for:

- Pulmonary embolism: 83.3% (strict), 97.2% (broad)
- Hemorrhagic stroke: 85.7% (strict & broad)
- Cardiac inflammatory disorders (myocarditis/pericarditis): 83.3%(strict & broad)

Moderate PPVs (60–80%) included:

- Non-hemorrhagic stroke: 72.4% (strict), 82.8% (broad)
- Immune thrombocytopenia (ITP): 75.0%(strict & broad)
- Guillain-Barré syndrome (GBS): 62.5% (strict), 100.0% (broad)
- Deep vein thrombosis (DVT): 60.0%(strict & broad)
- Transverse myelitis: 66.7%(strict & broad)

Low PPVs (<60%) were found for:

- Encephalitis/ADEM: 26.7%(strict & broad)
- Thrombosis with thrombocytopenia syndrome (TTS): 55.2%(strict & broad)
- Cerebral venus sinus thrombosis (CVST): 100% but was based on limited number of cases(strict & broad)

Table 1: PPVs for the studied AESIs

AESI	Data source	LOC1	LOC2	LOC3	LOC4a	LOC4b	LOC5	Total validated cases	Strict PPV(95% CI)	Broad PPV(95% CI)
Cardiac Inflammation	VID	4	10	6	0	9	4	33	83.33 (62.62-95.26)	83.33 (62.62-95.26)
CVST	SIDIAP	2	1	0	0	0	0	3	100 (29.24-100)	100 (29.24-100)
	VID	2	0	0	0	1	0	3	100 (15.81-100)	100 (15.81-100)
DVT	VID	14	0	7	0	15	14	50	60 (42.11-76.13)	60 (42.11-76.13)
Encephalitis (ADEM)	VID	4	0	0	0	0	11	15	26.67 (7.79-55.1)	26.67 (7.79-55.1)
GBS	VID	3	2	0	3	4	0	12	62.5 (24.49-91.48)	100 (63.06-100)
Hemorrhagic Stroke	VID	24	0	0	0	11	4	39	85.71 (67.33-95.97)	85.71 (67.33-95.97)
ITP	VID	3	3	0	0	2	2	10	75 (34.91-96.81)	75 (34.91-96.81)
Non-Hemorrhagic Stroke	VID	16	1	4	3	21	5	50	72.41 (52.76-87.27)	82.76 (64.23-94.15)
Pulmonary Embolism	VID	30	0	0	5	14	1	50	83.33 (67.19-93.63)	97.22 (85.47-99.93)
Transverse Myelitis	VID	0	1	1	0	0	1	3	66.67 (9.43-99.16)	66.67 (9.43-99.16)
TTS	SIDIAP	6	1	9	9	17	4	46	55.17 (35.69-73.55)	86.21 (68.34-96.11)
	VID	1	0	0	0	8	0	9	100 (2.5-100)	100 (2.5-100)

CONCLUSION

This study successfully applied a standardized validation framework to evaluate the diagnostic accuracy of AESI detection algorithms following Ad26.COV2.S (JCOVDEN) vaccination in two distinct European real-world data sources. Overall, PPVs varied substantially across AESIs, data sources (VID vs SIDIAP). High PPVs were achieved for conditions such as pulmonary embolism and hemorrhagic stroke, reflecting strong algorithmic performance in well-documented clinical contexts. Lower PPVs for TTS reflect that only the co-occurrence of thrombosis and thrombocytopenia was validated, not confirmed TTS, due to missing key laboratory/imaging data—highlighting the need for richer clinical information. These findings highlight the importance of validation tailored to data environment characteristics and support future investment in more granular clinical capture for regulatory-grade vaccine safety monitoring.

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VAC4EU Vaccine monitoring collaboration for Europe

Conflicts of interest

This study is funded by Janssen-Cilag International NV. The authors and their departments conduct research for government, public, and private organisations, including pharmaceutical companies, according to the ENCePP Code of Conduct. NP, and CW are employed by Johnson & Johnson and hold company stocks.

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