COVID-19 Vaccines and Adverse Events of Special Interest:

A multinational Global Vaccine Data Network (GVDN) signal-detection study

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Genesis of the GVDN

During the 2009 influenza pandemic, a possible risk of narcolepsy was identified following vaccination in Finland.

The subsequent response was not coordinated, and different countries found different levels of risk:

- 16-fold increased risk in Finland
- No increased risk in the Netherlands

It took six years for the CDC global SOMNIA study to provide results to inform public health decision making.

Clearly establishment of a global coordinated vaccine safety resource ready to respond to new concerns was warranted.

In 2021, GVDN commenced activities on the safety of COVID-19 vaccines.

Annecy, 2019

GVDN Partners and Collaborating Sites

6 continents | **26 countries** | **31 sites** | **>300 million people**

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World Largest COVID-19 Vaccine Safety Study

Category	Adverse Event of Special Interest (AESI)
Neurological Conditions	Guillain-Barré syndrome (GBS)
	Transverse myelitis (TRM)
	Facial (Bell's) palsy (BP)
	Acute disseminated encephalomyelitis (ADEM)
	Febrile seizures (FSZ)
	Generalized seizures (GSZ)
Haematological Conditions	Thrombocytopenia (THR)
	Idiopathic thrombocytopenia (ITP)
	Pulmonary embolism (PEM)
	Cerebral venous sinus thrombosis (CVST)
	Splanchnic vein thrombosis (SVT)
Cardiovascular Conditions	Myocarditis (MYO)
	Pericarditis (PER)

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COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals

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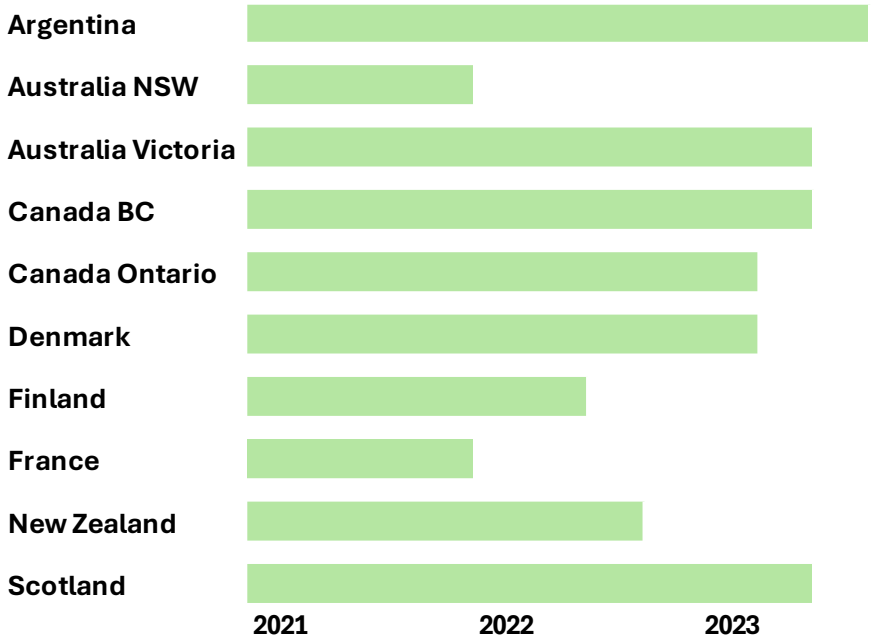
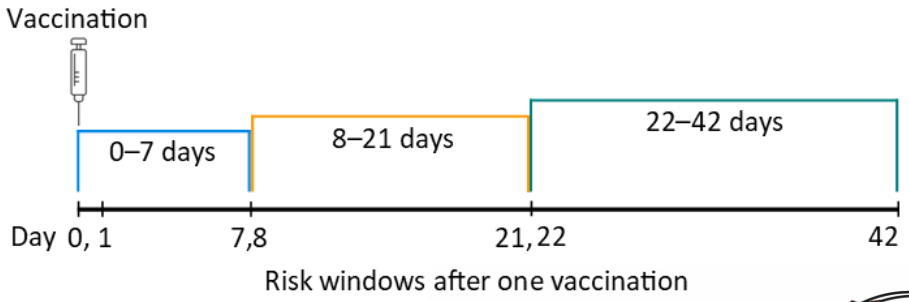
COVID-19 Vaccines

Vaccine platform	Vaccine brand	Total doses
Inactivated	Covilo or SARS-CoV-2 Vaccine (Vero Cell) [Sinopharm (Beijing)] BIBP	134,550
	Covaxin [Bharat Biotech] BBV	1,660
	CoronaVac or Sinovac [Sinovac Biotech] SINO	31,598
	Inactivated (Vero cell) [Sinopharm (Wuhan)] WIBP	623
Nucleic acid-based	Comirnaty or Riltozinameran or Pfizer/BioNTech COVID-19 Vaccine Bivalent [Pfizer/BioNTech] BIBNT	3,516,963
	Comirnaty or Tozinameran (original) [Pfizer/BioNTech or Fosun-BioNTech] BNT	**183,677,660**
	Comirnaty or Tozinameran Paediatric (original) [Pfizer/BioNTech or Fosun-BioNTech] PBNT	2,439,086
	Spikevax bivalent Original/Omicron [Moderna] BIMODO	2,750,476
	Elasomeran or Spikevax or TAK-919 Half Dose (original) [Moderna or Takeda] HMOD	400,395
	Elasomeran or Spikevax or TAK-919 (original) [Moderna or Takeda] MOD	**36,222,514**
Protein-based	MVC-COV1901 [Medigen] MVC	16
	Covovax or Nuvaxoid [Novavax or Serum Institute of India] NVX	66,856
Non-replicating viral vector	Convidecia or Convidence [CanSino] ADN	3,938
	Covishield or Vaxzevria [AstraZeneca or Serum Institute of India] AZD	**23,094,620**
	Sputnik Light or Gam-COVID-Vac [Gamaleya Research Institute] LGM	26
	Sputnik V [Gamaleya Research Institute] VGM	84,460
	Janssen [Janssen/Johnson & Johnson] JJJ	1,137,505

Study Population/Period





Risk windows after one vaccination

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Observed versus Expected Rates

- Pre-COVID-19 background rates in 2015-2019
  - 2019-2020 for Denmark due to change in hospital register
  - Patient types (ED, hospital inpatient/outpatient, primary care)
  - Stratified by sex and age groups (5-year, 10-year, 20-year)
- Expected rates within 42 days post-vaccination
  - Age-sex stratified person-years multiplied by corresponding background rates
  - Estimated by vaccine brand/dose profile (e.g. BNT1)
- Observed rates within 42 days post-vaccination
  - Aggregated counts on total vaccinated per AESI
- Observed vs expected (OE) rate ratios
  - 95% CI using Exact Poisson distribution
  - Prioritisation of signals (traffic light)

Red: LBCI* >1.5, statistically significant safety signal

Yellow: LBCI* >1 and ≤1.5, statistically significant

Green: LBCI* ≤1.0, not statistically significant

*LBCI: Lower bound of confidence interval

ADEM - Acute disseminated encephalomyelitis

CVST - Cerebral venous sinus thrombosis

AESI	Vaccine	OE Ratio (95% CI)
GBS	AZD1	2.49 (2.15, 2.87)
ADEM	MOD1	3.78 (1.52, 7.78)
CVST	AZD1	3.23 (2.51, 4.09)
MYO	BNT1	2.78 (2.61, 2.95)
	BNT2	2.86 (2.70, 3.03)
	BNT3	2.09 (1.88, 2.32)
	MOD1	3.48 (3.00, 4.01)
	MOD2	6.10 (5.52, 6.72)
	MOD3	2.01 (1.60, 2.49)
PER	MOD1	1.74 (1.54, 1.97)
	MOD4	2.64 (2.05, 3.35)
	AZD3	6.91 (3.45, 12.36)

Global Vaccine Data Network®

The Global Vaccine Data Network™ is a multinational collaboration ready to conduct globally coordinated epidemiological studies on the safety and effectiveness of vaccines, including COVID-19 vaccines.

Home / Data Dashboards / Observed vs. expected rates

https://www.globalvaccinedatanetwork.org/Data-Dashboards

Observed vs. expected rates

The *GVDN Observed vs. Expected Dashboard* below compares the occurrence of adverse events of special interest (AESI) from different sites/countries and population subgroups (age and sex) on a set of consistently defined AESI after the introduction of COVID-19 vaccines with the number of expected events based on background rates measured over 2015–2019 in the same population subgroups, prior to the SARS-CoV-2 virus (COVID-19 disease) outbreak and introduction of COVID-19 vaccines.

The *Dashboard* also presents data, under the *Global data (meta-analysis)* site, from meta-analyses of the combined (aggregated) observed vs. expected rates of AESI reported by the GVDN sites/countries. The use of common protocols across the sites/countries harmonises the approach to collection, collation, and analyses of data. This allows aggregation of the results from the locally measured observed number of cases compared with the number of expected events based on background rates measured over 2015–2019 in the same local population subgroups, prior to the SARS-CoV-2 virus (COVID-19 disease) outbreak and introduction of COVID-19 vaccines.

Click on this link to visit the *Background Rates Dashboard* on our website.

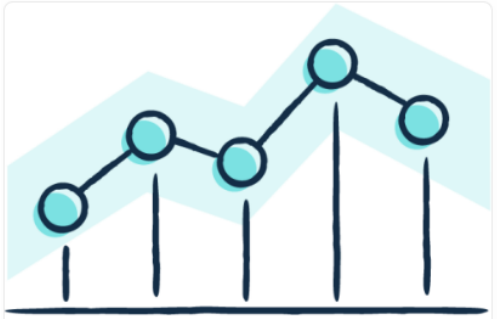
Click on this link to download the *GVDN Observed vs. expected analyses of COVID-19 vaccine adverse events of special interest study protocol*.

Click on this link to view the paper *COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals* published in the journal Vaccine.

Ten GVDN member sites in eight countries followed the protocol above and analysed data from national or regional healthcare databases covering 99 million people from Europe, Asia, North and South America, and Oceania. Meta-analyses of the observed rates of adverse events of special interest after COVID-19 vaccine introduction compared with the expected (background) pre-COVID-19 vaccine rates established in the GVDN Background Rates Study that includes such a large, diverse population increases the statistical power to identify rare but potential vaccine safety signals to inform when further investigation is required and enhances generalisability of what is known about vaccine safety.

Click on this link to view the accompanying paper *Acute disseminated encephalomyelitis and transverse myelitis following COVID-19 vaccination – A self-controlled case series analysis* published in the journal Vaccine.

The GVDN site in Victoria, Australia conducted a self-controlled case series study including 6.7 million vaccinated individuals to determine the relative incidence of two neurological adverse events of special interest following receipt of a COVID-19 vaccine.



Background Rates

Observed vs. Expected Rates

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GVDN: Observed vs Expected (OE) Dashboard

Global Vaccine Data Network

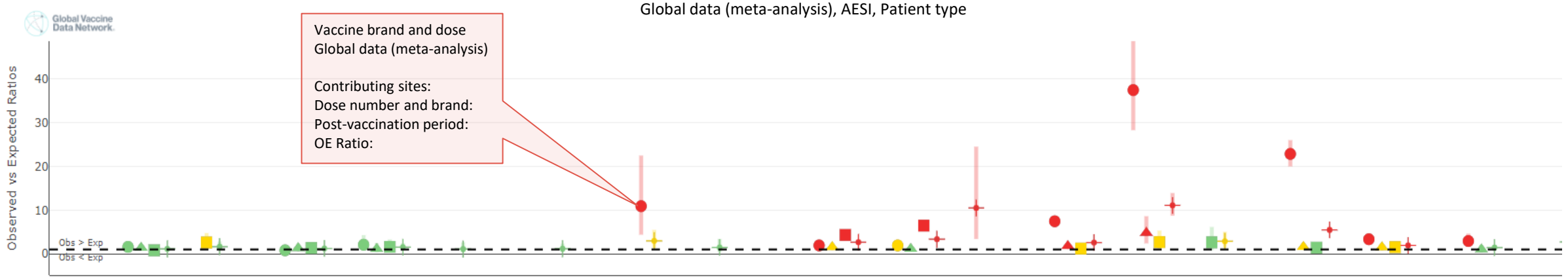
Site	AESI	Patient type	Vaccine platform	Vaccine brand profile	Post-vaccination period	Level of indication
Global data (meta-analysis)	Condition	All patients	12 items select	47 items selected	0-7 days, 8-21 days, 22-42 days, 0-42 days	4 items selecte

Graph | Table | Information

NOTE: Coloured bands indicate 95% confidence intervals of the OE ratios.

OE Ratio range : ○ 0-5 ○ 0-10 ○ 0-20 ◉ Full range

Global data (meta-analysis), AESI, Patient type



- *Note*: The coloured bands indicate 95% confidence intervals of the observed vs expected (OE) ratios
- For each AESI, and a given patient type, individual vaccine profiles are reported if the cumulative amount of follow up (in person-years) in the vaccinated population in the 0-42 days post-vaccination period is 10,000 or above.
- For each vaccine brand and dose profile, and post-vaccination period combination, the OE ratios and 95% confidence intervals (Lower_CI, Upper_CI) are suppressed if less than 5 events were observed (i.e. 1-4).
- The expected rates of AESI outcomes were calculated using the pre-COVID-19 vaccination background rates data from 2015-2019 (2019-2020 for Denmark), from the same population, collected in the GCoVS Background rates of adverse events of special interest following COVID-19 vaccination study.
- When the OE ratio is zero there are no observed counts and the confidence interval is not calculated.
- A 95% confidence interval above one (i.e. OE ratio = 1 the null hypothesis) suggests a higher than expected observed rate according to the vaccine brand and dose profile, and post-vaccination period, in the underlying population.
- Five levels of indication are defined: Dark gray (Zero counts/Suppressed values), Gray (Lower CI ≤1 and OE >5), Green (Lower CI ≤1 and OE ≤5), Yellow (Lower CI >1 and ≤1.5), Red (Lower CI >1.5).

Global Vaccine Data Network™. Observed vs Expected Dashboard. (Internet). Auckland - Thu 13:54:10; 13 Jul 2023 NZST

Meta-analysis was performed centrally by Global Coordinating Centre (GCC) and the results are presented on a live dashboard for all participating sites and overall

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Ongoing Vaccine Monitoring Studies

Study	Description
Background rates and Observed versus Expected rates of adverse events of special interest (AESI) – an updated study	• Annual incidence rates on a set of new AESI in 2015-2023 • New COVID-19 vaccines and other vaccines of interest (e.g. RSV) • Observed vs expected rates on population subgroups (sex and age groups)
Rapid Cycle analyses (RCA)	Conduct safety surveillance of newly introduced vaccines, vaccine variants or altered vaccination campaigns using different RCA sequential methods: • Self-control risk interval designs • Cohort designs using historical and concurrent comparators
Maternal and Neonatal Immunisation	• Estimate background rates of selected maternal, fetal, obstetric, and neonatal outcomes, as well as AESI during pregnancy in 2017-2023 • Evaluate the safety of COVID-19 vaccination in pregnant women and their neonates on pre-specified maternal, fetal, neonatal outcomes and AESI
Genomics of COVID-19 vaccine-induced GBS, VITT, and myocarditis/pericarditis	• Confirmed cases with first diagnosed GBS, vaccine-induced thrombosis and thrombocytopenia (VITT), or myocarditis/pericarditis within 42 days post-vaccination vs. healthy vaccinated controls as comparator • Association between genetic variants and COVID-19 vaccine-related AESI
Rapid response investigation (RRI) of a potential signal of concern or adverse event causing concern	• A rapid response investigation of potential signals of concern (SOC) and emergent adverse events causing concern (AEC) • Describe criteria required to initiate a RRI and the process to follow when SOC and AEC are identified for any vaccine of interest

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- Co-authors of the WCE conference abstract and presentation:

  Daniel Walsh, Kristyna Faksova, Anastasia Phillips, Helen Petousis-Harris, Jim Buttery, Steve Black, Anders Hviid

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