Assessment of the Risk of 32 Adverse Effects of Special Interest following COVID-19 Vaccination in the whole French population

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BACKGROUND

- Vaccines against COVID-19 have been administered to hundreds of millions of people worldwide.
- Numerous studies have assessed their safety, often investigating alerts released by health authorities.
- However, several signals suggested by published case reports remain unassessed.

OBJECTIVE

- To assess the risk of 32 acute adverse events of special interest (AESI), prespecified by the European Medicines Agency, following COVID-19 vaccination in the French population.

METHODS

- The study population was extracted from the French National Healthcare Data System (SNDS) covering 67 million people, among all patients with a rare AESI (frequency (f) ≤1.5/100 000 person-years (PY) and a 10% sample for others AESI (f>1.5/100 000 Person-Years).
- Only patients who experienced an incident acute AESI across auto-immune, cardiovascular, hematological, metabolic or neurological outcomes and who received ≥1 dose of COVID-19 vaccine in 2021 were analysed.
- Self-controlled risk interval (SCRI) analyses were used to compare, for each AESI, the incidence rate during an interval defined as at-risk following vaccination and the incidence rate during a control interval.
- Risk and control intervals were unique for a patient, specific to each AESI, of equal length, and separated by a 30-day washout period without overlapping of vaccine doses.
- Analyses were conducted by vaccine brand and platform.
- Incidence rate ratios (IRR) were estimated using conditional Poisson regression models with a 95% confidence interval (95% CI).

RESULTS

Table 1. Characteristics of sample population

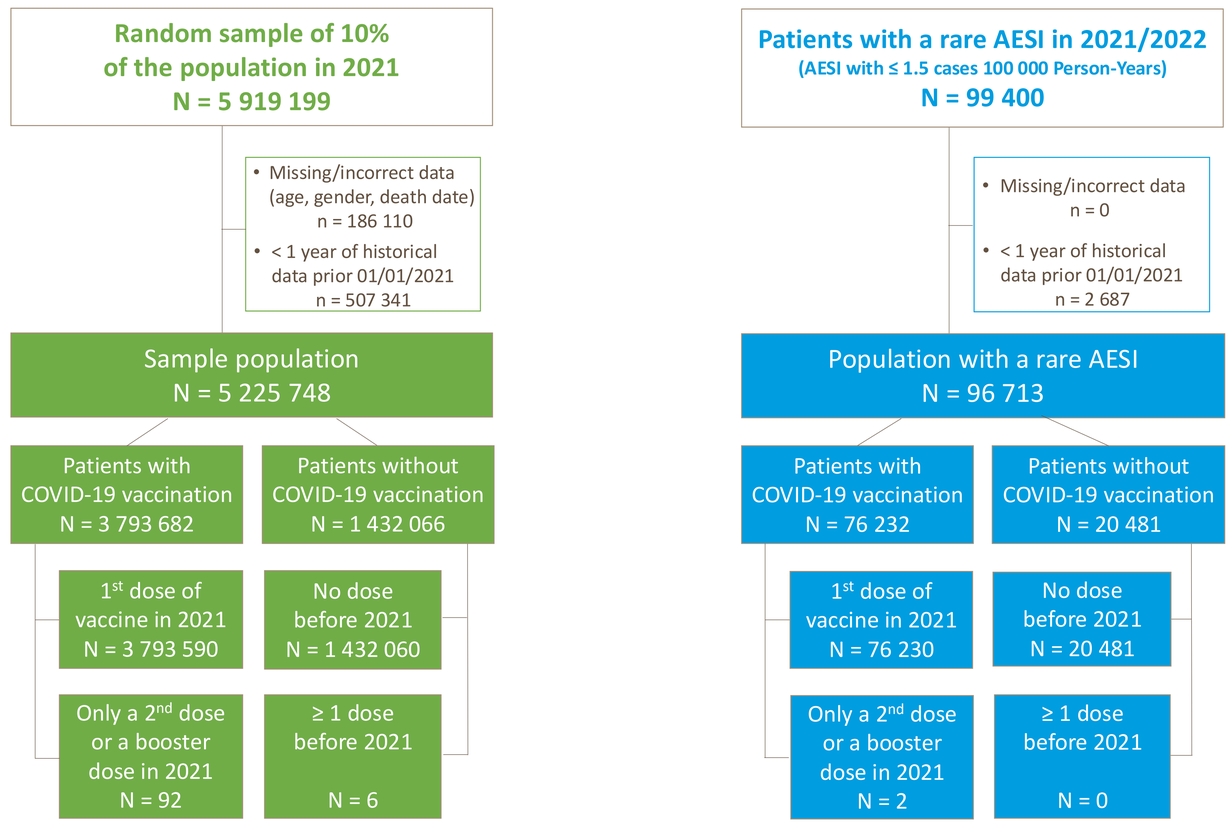
	Sample population		
	Male n= 2 547 594	Female n= 2 678 154	Total n= 5 225 748
Sex, %	48.8	51.2	100.0
Age, median (years)	41.0	44.0	43.0
Main comorbidities during 4-year pre-index period* (several answers possible), %			
Cardio/Cerebrovascular disease	26.2	29.1	27.7
Chronic respiratory disease	22.4	25.8	24.1
Mental health disease	10.8	18.6	14.8
Diabetes (type 1 or 2)	6.8	5.7	6.3
COVID-19 vaccine, % (2021)	71.1	74.0	72.6
mRNA BNT162b2	77.6	79.0	78.3
mRNA-1273	11.3	10.9	11.1
Adenoviral-vector ChAdOx1	9.0	8.2	8.6
Ad26.COV2.S	2.1	1.9	2.0

* 4 year preceding the start of studied year (01/01/2021), index date included

Disclosure:
The authors affiliated to Bordeaux PharmacoEpi are researchers from the BPE platform of the University of Bordeaux and its subsidiary the ADERA (MAB, CDP, JJ, PB, NHT), which performs financially supported studies for public and private partners in compliance with the ENCePP Code of Conduct.
This study has been labeled as a National Research Priority by the National Orientation Committee for Therapeutic Trials and other researches on Covid-19 (CAPNET). The investigators would like to acknowledge ANRS | Emerging infectious diseases for their scientific support, the French Ministry of Health and Prevention and the French Ministry of Higher Education, Research and Innovation for their funding and support.

RESULTS

- **Figure 1. Data analysis identification and selection of a 10% random sample population and patients with a rare adverse event of special interest (AESI)**



- **Table 2. Incidence rate ratio (IRR) comparing incidence rates of each AESI between risk time interval post-COVID-19 vaccination and control time interval cohort in sample or rare AESI populations, stratified by type of vaccine – Conditional Poisson regression models (SCRI)**

	AESI type	mRNA vaccines IRR [95% CI]	Adenoviral-vector vaccines IRR [95% CI]
	Auto-immune diseases		
	Guillain-Barré Syndrome	0.94 [0.49 ; 1.83]	3.00 [0.61 ; 14.86]
	Acute disseminated encephalomyelitis	**10.00 [1.28 ; 78.12]**	1.00 [0.06 ; 15.99]
	Thrombocytopenia	1.12 [0.81 ; 1.54]	2.50 [0.49 ; 12.89]
	Cardiovascular system: Acute cardiovascular injury		
	Microangiopathy	**1.41 [1.01 ; 1.97]**	3.50 [0.73 ; 16.85]
	Heart failure	1.00 [0.92 ; 1.09]	0.96 [0.68 ; 1.34]
	Coronary artery disease (CAD)	1.11 [0.99 ; 1.26]	0.94 [0.64 ; 1.38]
	Arrhythmia	1.00 [0.92 ; 1.09]	1.22 [0.93 ; 1.60]
	Myocarditis or Pericarditis	**1.95 [1.41 ; 2.69]**	1.17 [0.39 ; 3.47]
	Myocarditis alone	**3.51 [3.02 ; 4.08]**	1.42 [0.68 ; 2.97]
	Circulatory system: Coagulation disorder		
	Disseminated intravascular coagulation (DIC)	**2.08 [1.07 ; 4.03]**	-
	VTE	1.13 [0.98 ; 1.32]	1.30 [0.76 ; 2.25]
	Thrombotic microangiopathy	1.20 [0.81 ; 1.77]	1.50 [0.25 ; 8.98]
	Hemorrhagic stroke	**1.32 [1.05 ; 1.66]**	1.40 [0.62 ; 3.15]
	Ischemic stroke	1.07 [0.96 ; 1.20]	1.00 [0.71 ; 1.41]
	Cerebral venous sinus thrombosis (CVST)	**1.87 [1.31 ; 2.67]**	**3.20 [1.17 ; 8.73]**
	Thrombotic thrombocytopenia syndrome	-	-
	Single Organ Cutaneous Vasculitis	1.20 [0.89 ; 1.61]	1.33 [0.56 ; 3.16]
	Nerves and central nervous system		
	Generalized convulsion	1.13 [0.89 ; 1.44]	0.69 [0.30 ; 1.62]
	Meningoencephalitis	1.16 [0.96 ; 1.40]	1.24 [0.65 ; 2.34]
	Transverse myelitis	0.83 [0.36 ; 1.93]	1.00 [0.06 ; 15.99]
	Acute respiratory distress syndrome	1.19 [0.84 ; 1.70]	1.14 [0.41 ; 3.15]
	Skin and mucous membrane, bone and joints system		
	Erythema multiforme	2.50 [0.78 ; 7.97]	-
	Chilblain – like lesions	2.00 [0.50 ; 8.00]	-
	Other system		
	Anosmia ageusia	0.92 [0.40 ; 2.08]	-
	Anaphylaxis	6.00 [0.72 ; 49.84]	-
	MISC-C	-	-
	Death		
	Death (any causes)	**0.10 [0.08 ; 0.12]**	**0.08 [0.04 ; 0.19]**
	Sudden death	0.75 [0.17 ; 3.35]	-
	COVID-19 (positive test or hospitalization)	**1.11 [1.09 ; 1.12]**	**1.51 [1.40 ; 1.62]**
	AESI without BGR for comparison		
	Bells' palsy	1.00 [0.49 ; 2.05]	-
	Kawasaki disease	-	-
	Acute pancreatitis	1.12 [0.90 ; 1.40]	2.14 [0.87 ; 5.26]
	Rhabdomyolysis	**1.34 [1.03 ; 1.74]**	1.00 [0.48 ; 2.10]
	Severe Cutaneous Adverse Reactions (SCARs)	-	-

Sample Population Rare AESI Population

CONCLUSIONS

- **These analyses relying on a large population-based database strengthen safety signals associated with COVID-19 vaccines that remain to be investigated.**
- **Comparative cohort designs are ongoing to refine these signals and provide reliable risk quantification.**

ISPE's 41st Annual Meeting, scheduled for August 22-26 2025 at Washington DC Convention Center, USA

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