Neurological complications of vaccination

배 종 석
한림의대 강동성심병원

FAQs in clinics

- 47/F, RRMS on long-term DMT
  - First event, 5 years ago, after vaccination
  - "Do I have to get vaccinated for COVID-19?"
  - "Do I have to vaccinate my father in nursing home?"
  - "Do I have to vaccinate my daughter? And…"

http://www.koreams.org/sub/faq.php?cate=lib_faq_covid

https://www.ninds.nih.gov/Current-Research/Coronavirus-and-NINDS/nervous-system

Message from NINDS

Does the COVID-19 vaccine cause neurological problems?

Almost everyone should get the COVID-19 vaccination. It will help protect you from getting COVID-19. The vaccines are safe and effective and cannot give you the disease. Most side effects of the vaccine may feel like flu and are temporary and go away within a day or two. In early vaccine development, there were extremely rare reports of unexplained neurological illness following COVID-19 vaccination, but regulators found no evidence the vaccines caused the illness. The U.S. Food and Drug Administration (FDA) continues to investigate any report of adverse consequences of the vaccine and none have appeared as of yet. Consult your primary care doctor or specialist if you have concerns regarding any pre-existing known allergic or other severe reactions and vaccine safety. Scientists are studying the risk to benefit ratio of the vaccine in someone who previously developed Guillain Barré syndrome after a vaccination. The general sense is the COVID-19 vaccine is safe in individuals whose Guillain-Barré syndrome was not associated with a previous vaccination.

The U.S. Centers for Disease Control and Prevention (CDC) site offers information on vaccine resources at https://www.coronavirus.gov/. The National Institutes of Health (NIH) has information on vaccines for the coronavirus. See: https://covid19.nih.gov/

Goss AL et al. Ann Neurol. 2021 (in press)

Message from ANA

- **ANA Investigates Detection & Management of Neurologic Complications from COVID-19 Vaccines**

Less than a year -- that's how long it took between when the novel coronavirus emerged and when a vaccine was available to prevent it. This incredible speed of vaccine development exemplifies scientific innovation in a time of crisis. There is increasing vaccine acceptance among the public, but questions about target populations, mechanisms, and side effects remain. Neurological complications are well-documented with other vaccines, and some have already been seen with the vaccines for Covid-19. Our guest on this episode, Dr. Avindra Nath, is a physician-scientist who specializes in neuroimmunology and infections of the nervous system. He is the intramural Clinical Director of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health. The resources mentioned during the episode may be accessed on: https://myana.org/education/ana-investigates-podcast-series. Series 2, Episode 4

- No neurological condition is a contraindication to COVID-19 vaccination, but there are special considerations around COVID-19 vaccines for patients who take immunosuppressive medications.
  - Increased risk for severe COVID-19, making vaccination particularly important.
  - Some of these immunosuppressive medications may attenuate immune responses to vaccine antigens.
  - Patients with MS taking certain DMT suggest timing the vaccine to before the start of treatment or near the end of a treatment cycle.
- Overall, both at an individual and a population level, the benefits of COVID-19 vaccination far outweigh the risks of a neurological complication.
- Prospective research will be needed to establish any association between COVID-19 vaccines and neurological complications, particularly as new strains of the virus emerge and new vaccines are developed to combat them.

Vaccine Adverse Effect Report System (VAERS)

- Database open to the public
- Standardized coding (COSTART)
- 1300 terms, searchable
- Most common neurological 9442 symptoms include (2021/03/02)
  - Dizziness, headache, tinnitus
  - Pain, muscle spasms, myalgia & paresthesia
  - Rare cases of tremor, diplopia, dysphonia,
  - Seizures
  - Reactivation of herpes zoster
- Neurological disorders
  - Stroke (17), GBS (32), ADEM (6), myelitis (9), facial palsy (190)

- Limitations
  - Incomplete data
  - Diagnoses not verified
  - Temporal does not equal casual
  - Can not be used for true incidence rates
  - Faulty numerators and denominators
  - Reporting bias
  - Can not be used for calculating true relative risks
  - Primarily hypothesis generating

The "urban myth" of the association between neurological disorders and vaccinations

- Causality or casualness?
  - A severe neurological disease may arise simply by chance after the administration of a vaccine.
- Anti-vaccination activism
  - 1998, Lancet MMR autism fraud
  - Andrew Wakefield

- A true "urban myth"
  - Autism - MMR
  - Multiple sclerosis - HBV
  - Alzheimer disease – influenza
  - Optic neuritis - TDaP
  - Inflammatory bowel disease
  - SIDS
  - Diabetes
  - Asthma
  - Attention Deficit Disorder
  - Infantile Spasms

Gasparini R et al. J Prev Med Hyg 2015; 56: E1–8.

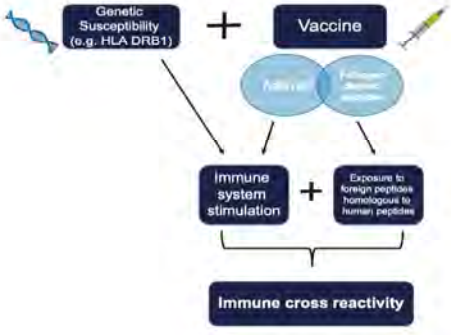
Historical concerns about vaccine safety

Incident	Year	Consequence	Reference
Cutter Incident	1955	Started a polio epidemic. Two production pools accounting for 120,000 doses made by Cutter Laboratories caused 40,000 cases of polio; 51 were paralyzed, and five killed even though the vaccine had passed safety testing.	Offit, 2005
Simian Virus 40 (SV40)	1955 to 1963	From 1955 to 1963, an estimated 10-30% of polio vaccines administered in the US were contaminated with SV40, leading to the development of a certain type of cancer.	Stratton *et al.*, 2002
Respiratory Syncytial Virus (RSV)	1966	Of the 20 children who underwent the FI-RSV vaccine trial, 16 needed hospitalization, two died afterwards. On contrary, only one of the 21 control group participants was hospitalized. FDA promptly suspended all clinical trials.	Kim *et al.*, 1969
H1N1 Swine Flu Vaccine and Guillain-Barré Syndrome (GBS)	1976	Increased risk of GBS, a rare neurological disorder.	Schonberger *et al.*, 1979
Hepatitis B Vaccine (HBV) and Multiple Sclerosis (MS)	1998	A relationship between HBV vaccine and MS has been suggested but is disputed.	Ascherio *et al.*, 2001; Naismith and Cross, 2004; Le Houézec, 2014
Rotavirus Vaccine and Intussusception	1998 to 1999	Suspension after 15 cases of intussusception, a bowel obstruction in which one segment of bowel becomes enfolded within another segment.	Iskander *et al.*, 2004
H1N1 Influenza Vaccine and Narcolepsy	2009 to 2010	Concern raised after abrupt-onset childhood narcolepsy was seen in Finland in 2010, but not observed in other countries including in the USA.	Partinen *et al.*, 2012; Duffy *et al.*, 2014
Dengue Virus Vaccine-Dengvaxia	2017	Excess risk of severe dengue in seronegative vaccine recipients compared to seronegative non-vaccinated individuals. The Philippines stopped their immunization program after getting this warning.	Wilder-Smith, 2020

Haidere MF et al. Biomol Ther (Seoul) 2021; 29: 1–10.

Segal Y et al. Cell Mol Immunol 2018; 15: 586–594.

Vaccine-induced autoimmunity



- Biological plausibility vs unexpected event
- The role of molecular mimicry and immune cross reaction

Table 1 Examples of vaccines associated with immunological crossreaction and the suspected molecular elements implicated

Vaccine	*Autoimmune disease*	*Suspected viral element implicated*	*Suspected homologous human target*	*References*
H1N1	Narcolepsy	NP	HCRT receptor	39
	GBS	HA	GM1	46
HBV	MS	SHBsAg	MOG	78
		HBV polymerase	MBP	78
HPV	SLE	HPV L1 peptides	NK receptors	93,94
			Complement components	
	POTS	HPV L1 peptides	Cardiac myosin/adrenergic receptors	105,116,118

General aspects

1. Nearly all vaccines cause some adverse events, but most adverse events are mild.
2. Licensed vaccines are generally safe, nevertheless, constant vigilance is needed to investigate for new problems.
3. There is poor understanding of causality assessment, so we need to find improved methods to communicate adverse event data.
4. Rare diseases will inevitably occur by chance during the vaccination window, and that the temporal association between vaccination and GBS onset even in large numbers of individuals within a huge population of billions is not adequate evidence of causation.
5. Although, to date, there has not been a clear signal suggesting higher rates of neurological disease associated with the COVID-19 vaccines, public tolerance to adverse events or fear for them are minimal.

GBS & influenza vaccine

- 1918 Spanish flu
- 1976 US swine influenza (1976/77 USA/New Jersey/76 program) vaccine
  - 35 million dose
  - GBS: 532 (vaccinated) /1098 (unvaccinated) during 4 months
  - Calculated RR of 7.6 (95% CI 6.7–8.6) in the 6 weeks
  - Risk of one case per 100,000
  - Suspension of the vaccine program
- 2009 H1N1 influenza
  - Incidence rate ratio 2·35, 95% CI 1·42–4·01, p=0·0003
  - Risk of 1.6 excess cases of GBS per 1,000,000

Stowe J et al. CNS Drugs 2020; 34: 1–8.

Stowe J et al. CNS Drugs 2020; 34: 1–8.
Keddie S et al. Brain 2021: 144; 357–371

GBS & other vaccine

- Human papilloma virus, Hepatitis B, polio, tetanus, meningococcus, rabies, & orally administered adenovirus vaccine.
- No causative links have been conclusively proven despite these individual reports being widely quoted.

COVID-19 vaccine and Guillain-Barré syndrome: let's not leap to associations

This special commentary refers to 'Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome' by Keddie *et al.* (doi:10.1093/brain/awaa433).

A worldwide mass vaccination campaign to control the COVID-19 pandemic is imminent. Understanding the epidemiology of rare diseases whose onset will inevitably occur by coincidence following SARS-CoV-2 vaccination, but which have little to no evidence of being caused by them in resulting in unnecessary morbidity and mortality.

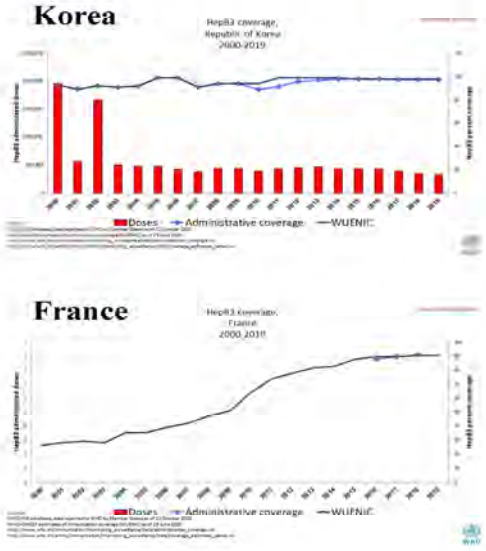
Global cases of the COVID-19 respiratory illness caused by the virus SARS-CoV-2 have surpassed 50 million, with a pandemic resulting in medical and economic devastation worldwide. As of late November 2020, four vaccines involving over 100 000 participants have displayed favourable efficacy without significant reported side effects in phase 3 trials. At least 57 COVID-19 vaccines are in phase 1–3 trials; six already have limdisorder resulting in severe and sometimes lasting paralysis; about one-third of patients develop respiratory failure requiring intensive care unit (ICU) admission and ventilation (Leonhard *et al.*, 2019). GBS is fatal in 3–5% of patients, and about two-thirds have residual disability. The lifetime individual risk of acquiring GBS is about 1:1000, and the annual incidence of GBS is ~1.7 persons per 100 000 population (Sejvar *et al.*, 2011; Keddie *et al.*, 2021). Some 1500 cases of GBS are recorded in the UK each year, or

MS & Hepatitis B Vaccine

- 1994 France
  - MS with onset or relapse
  - Suspension of vaccine program
  - Still in vaccination hesitancy in France
- 2004, UK
  - 163 cases of MS and 1,604 controls.
  - The OR of MS for vaccination within 3 years: 3.1 (95% CI 1.5, 6.3).
  - No increased risk of MS was associated with tetanus and influenza vaccinations.
  - Unable to adjust for all risk factors
  - No routine hepatitis B vaccination program & record
- 2018 SR
  - MS: 1.19 (95% CI 0.93–1.52)
  - Central demyelination: 1.25 (95% CI 0.97–1.62)

Stowe J et al. CNS Drugs 2020; 34: 1–8.

MS & Hepatitis B Vaccine (Cont.)



- **By WHO**
- **Infodemic**: "an overabundance of information and the rapid spread of misleading or fabricated news, images, and videos."
- **Disinformation**: "false information created with the intention of profiting from it or causing harm."
- **Vaccine hesitancy**: "the reluctance or refusal to vaccinate despite the availability of vaccines".

Farooq F et al. J Korean Med Sci 2021; 36: e78.

MS & Hepatitis B Vaccine (Cont.)

- Consensus
  - MS cannot be caused by vaccines, neither by inactivated nor by live vaccines.
  - In immunocompromised patients, live vaccines may lead to a stronger immune reaction.
  - Vaccination should be controlled in patients who have been vaccinated while receiving immunomodulatory or immunosuppressive treatment..
  - There is evidence that systemic infections can worsen MS, thus vaccination will lower the risk of relapses by reducing the risk of infections. Therefore, vaccination should be in general recommended to MS patients.

Stowe J et al. CNS Drugs 2020; 34: 1–8.

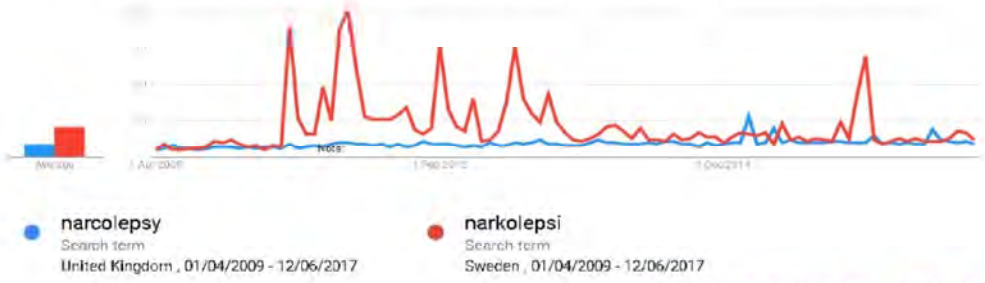
Narcolepsy & Pandemrix™

- 2010, Finland and Sweden
  - Study in Finland reported a 13-fold increased risk of narcolepsy following Pandemrix™ in children aged 4–19 years
  - The majority of whom had onset within 3 months of vaccination and almost all within 6 months
- 2013, UK
  - A 14-fold increased risk in those vaccinated with Pandemrix™
  - Attributable risk: 1.9 per 100,000 doses
  - Even in a country of low vaccine coverage was low, the association can be demonstrated using robust epidemiological methods.

Stowe J et al. CNS Drugs 2020; 34: 1–8.

Narcolepsy & Pandemrix™ (Cont.)

- Lessons from this issue
  - An epidemiological challenge in terms of identifying the cases and their vaccine histories in a non-biased manner
  - The awareness of the hypothesized association is more important than recognition of admission
  - Public awareness vs professional awareness
  - No association has been seen with other pandemic or seasonal vaccines



Stowe J et al. CNS Drugs 2020; 34: 1–8.

Voysey M et al. Lancet 2021; 397: 99–111.

Myelitis & AZ vaccine

Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK

- Two patients developed transverse myelitis after receiving the Oxford/AstraZeneca vaccine.
  - 14 days after ChAdOx1 nCoV-19 booster vaccination as being possibly related to vaccination, considering the most likely diagnosis to be of an idiopathic, short segment, spinal cord demyelination.
  - One case was ultimately deemed unlikely to be related to vaccination (the patient had pre-existing MS)

Nervous system disorders	**7 (0.1)**	**7**	**4 (<0.1)**	**4**
Facial spasm	1 (<0.1)	1	0	0
Ischaemic stroke	1 (<0.1)	1	0	0
Migraine	1 (<0.1)	1	0	0
Multiple sclerosis	1 (<0.1)	1	0	0
Myelitis	0	0	1 (<0.1)	1
Myelitis transverse	1 (<0.1)	1	0	0
Presyncope	1 (<0.1)	1	0	0
Serotonin syndrome	1 (<0.1)	1	0	0
Subarachnoid haemorrhage	0	0	1 (<0.1)	1
Syncope	0	0	1 (<0.1)	1
Transient ischaemic attack	0	0	1 (<0.1)	1

Baxter R et al. Clin Infect Dis 2016; 63: 1456–1462.

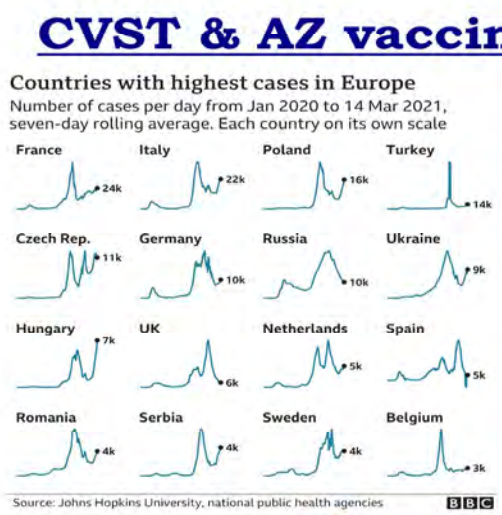
Myelitis or ADEM & vaccination

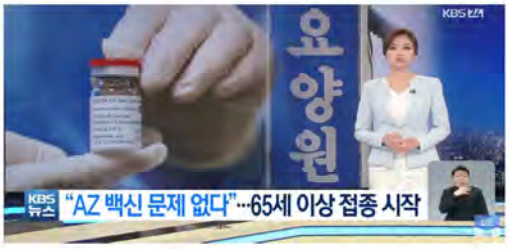
- Following nearly 64 million vaccine doses, only 7 cases of TM and 8 cases of ADEM were vaccinated during the primary exposure window 5–28 days prior to onset.
- Tdap exposure 5–28 days prior to ADEM onset was 15.8 (95% con!dence interval [CI], 1.2–471.6; P = .04)

Table 3. Relative Risk[a] of Acute Disseminated Encephalomyelitis in the 5- to 28-Day Risk Interval Following Vaccines, Compared to Remainder of the 9 Months After Vaccination—Vaccine Safety Datalink, 2007–2013

	Cases		Comparison Risk Sets: Informative Cases and Noncases[b]				
Vaccine Type	No.	% in Exposure Interval	No.	% in Exposure Interval	Adjusted Odds Ratio	(95% CI)	*P* Value
MMR	6	33.3	46 482	10.1	5	(.6–29.9)	.12
IPV	1	0	6025	6.6	0	(.0–270.1)	.93
PCV7	3	0	39 788	4.5	0	(.0–48.1)	.87
MCV4 (Sanofi)	3	0	14 731	9	0	(.0–18.0)	.76
Tdap	3	66.7	9972	11.5	15.8	(1.2–471.6)	.04
DTaP/IP/Hib	2	0	5387	7.9	0	(.0–40.7)	.85
Zoster	1	0	3226	9.9	0	(.0–173.1)	.9
DTaP/IP	4	25	29 751	8.9	4.1	(.1–44.0)	.32
PCV13	3	33.3	7047	22.8	3.6	(.1–95.4)	.49
DTaP	1	0	6153	6.6	0	(.0–270.4)	.93
Varicella	6	33.3	44 953	10.5	4.3	(.5–25.4)	.14
MPSV4	1	100	3	33.3	NE	(.1 to . . .)	.33
PPSV23	3	0	13 359	10.3	0	(.0–14.5)	.71
HPV4	6	16.7	56 846	12.1	1.5	(.1–10.7)	.7
MMR-Varicella	1	0	2046	6.1	0	(.0–292.0)	.94
Any MCV4	3	0	16 157	9.1	0	(.0–17.5)	.75
Any PCV	6	16.7	46 862	7.3	2.8	(.1–21.2)	.4
H1N1	6	0	56 953	1.3	0	(.0–102.7)	.95
HAV	8	12.5	60 878	7.5	1.9	(.1–13.0)	.54
HBV	2	0	2112	2.4	0	(.0–128.7)	.95
Hib	3	0	18 285	6.8	0	(.0–25.3)	.8
IIV	21	19	281 468	7	1.5	(.4–5.0)	.53
LAIV	4	0	2650	12.6	0	(.0–4.9)	.34
Td	1	0	155	1.9	0	(.0–962.7)	.98
Any	47	17	813 498	8.8	1.7	(.7–3.8)	.19

CVST & AZ vaccine





EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Search

Medicines | Human regulatory | Veterinary regulatory | Committees | News & events | Partners & networks | About us

COVID-19 Vaccine AstraZeneca: benefits still outweigh the risks despite possible link to rare blood clots with low blood platelets

CVST & AZ vaccine (Cont.)

Information for healthcare professionals

- Mesenteric vein or cerebral vein/cerebral venous sinus thrombosis
- 14 days after vaccination, women under 55
- Causality although not confirmed, cannot therefore be excluded.
- The strength of any association is uncertain.
- EMA considers that the benefit-risk balance of the medicine remains positive.
- Update on SmPC with information on DIC & CVST
- Healthcare professionals are urged to be alert for possible cases of thromboembolism, DIC or CVST occurring in vaccinated individuals.
- Recipients should be warned to seek immediate medical attention for symptoms of thromboembolism, and especially signs of thrombocytopenia and cerebral blood clots such as easy bruising or bleeding, and persistent or severe headache, particularly beyond 3 days after vaccination.

https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots

Summary

1. The answer to the question of whether vaccination can cause neurological disease is multifaceted.
2. The evidence does not support an association between MS and the hepatitis vaccine, while for GBS and influenza vaccines the evidence suggests a small increased risk though it is much smaller than the risk from a natural influenza virus infection.
3. The established association between narcolepsy and Pandemrix™ should act as a lesson for the vaccine safety community that sometimes unexpected but serious conditions can arise and need to be investigated rapidly however biologically implausible.
4. As the experience with narcolepsy has shown, not all vaccine safety concerns can be anticipated on the basis of biologically plausible and thus predictable effects.
5. As new vaccines are introduced, the basis of discussions on vaccine safety should be the acceptance that vaccination can carry a small risk but that this risk needs to be balanced against the enormous individual and public health benefits.